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ABSTRACT BOOK

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C001

FROM HIGH DIMENSIONAL DATA TO DISEASE MECHANISMS – NOTCH SIGNALLING IN HODGKIN LYMPHOMA

Köchert K, Kreher S, Aster JC, Kitagawa M, Jöhrens K, Anagnostopoulos I, Jundt F, Stein H, Janz M, Dörken B, Mathas S

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Inappropriate activation of the NOTCH signaling pathway, e.g. by activating mutations, contributes to the pathogenesis of various human malignancies. Using a bottom up approach based on the acquisition of high dimensional microarray data of classical Hodgkin lymphoma (cHL) and non-Hodgkin B cell lymphomas as control, we identify a cHL specific NOTCH gene-expression signature dominated by the NOTCH coactivator MAML2. We thus further analysed the role of MAML2 in the context of aberrant NOTCH signaling in B cell lymphomas. Statistical analyses of the acquired microarray data led to the discovery of a cHL MAML2 dominated NOTCH gene-expression signature. This set the basis for demonstrating that aberrant expression of the essential NOTCH co-activator Mastermind-like2 (MAML2) provides an alternative mechanism to activate NOTCH signaling in human lymphoma cells. Using immunohistochemistry we detected high-level MAML2 expression in several B cell-derived lymphoma types, including cHL cells, whereas in normal B cells no staining for MAML2 was detectable. Inhibition of MAML protein activity by a dominant negative form of MAML or by shRNAs targeting MAML2 in cHL cells resulted in down-regulation of the NOTCH target genes HES7 and HEY1, which we identified as overexpressed in cHL cells, and in reduced proliferation. In order to target the NOTCH transcriptional complex directly we developed short peptide constructs that competitively inhibit NOTCH dependent transcriptional activity as demonstrated by NOTCH reporter assays and EMSA analyses. We conclude that NOTCH signalling is aberrantly activated in a cell autonomous manner in cHL. This is mediated by high-level expression of the essential NOTCH coactivator MAML2, a protein that is only weakly expressed in B cells from healthy donors. This high-level expression is also found in other B cell associated malignancies. Using short peptide constructs we moreover show, that this approach is promising in regard to the development of NOTCH pathway inhibitors that will also work in NOTCH associated malignancies that are resistant to -secretase inhibition.

C002

THE ROLE OF MIRNAS IN HODGKIN LYMPHOMA

van den Berg A, Ping Tan L, Gibcus J, Kluiver J, Slezack-Prochzka I, Halsema N, de Jong D, Kroesen B-J, Poppema S

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Several studies indicate that HRS cells display a characteristic miRNA expression profile. Based on cell line profiling we demonstrated a high expression of miR-15, miR-16, miR-29, miR-155 and miR-17~92. Using miRNA in situ hybridization (ISH) we confirmed expression of miR-17-5p, miR-24, miR-106a, miR-146a, miR-155, miR-181b and miR-210 in the HRS cells in HL tissue. In contrast to the HL cell lines, expression of miR-21 was low in HRS cells of HL tissue, whereas expression level of miR-150 was very high. To investigate the role of miRNAs in the pathogenesis of HL we identified miRNA target genes in two HL cell lines by immunoprecipitation (IP) of the Ago2 containing RISC and the subsequent microarray analysis of the co-immunoprecipitated target genes. The miRNA-targetome of HL comprises about 2,500 genes. Gene ontology (GO) analysis for the total miRNA-targetome of HL showed a significant enrichment of genes involved in the regulation of apoptosis, immune system development, the NF-kB cascade and cell cycle. The miRNA-targetome of HL contained several genes known to be mutated in HRS cells, including A20, FAS, NFKB1A, NFKB1E, PERP and SOCS1. Only two (i.e. MYBL1 and CXCR4) of the loss-of-B-cell-phenotype signature genes were enriched in the IP-fraction suggesting that miRNAs do not play an important role in the downregulation of these genes. Inhibition of the anti-miR-17 seed family revealed that about 500 of the HL miRNA-targetome were regulated by miRNAs of the miR-17 seed family. One of the cell cycle genes targeted by the miR-17 seed family was CDKN1A coding for the p21 protein. We showed that CDKN1A is a valid target for this miRNA seed family although the effects on both protein and mRNA levels were limited. The G1-trap assay showed a clear increase in cells in the G1 phase upon inhibition of the miR-17 seed family in KM-H2 cells, whereas the effect was more limited in two other HL cell lines. In conclusion, we confirmed expression of miRNAs in the HRS cells of HL tissue and identified 2,500 genes that were regulated by miRNAs in HL. These genes were involved in deregulation of apoptosis, cell cycle, and NF-kB pathways.

C003

METHYLATION PROFILING OF MEDIASTINAL GRAY ZONE LYMPHOMA REVEALS A DISTINCTIVE SIGNATURE WITH ELEMENTS SHARED BY CLASSICAL HODGKIN'S LYMPHOMA AND PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

Eberle FC,[1] Rodriguez-Canales J,[1] Wei L,[2] Hanson JC,[1] Killian JK,[3] Sun H-W,[4] Adams LG,[3] Hewitt SM,[1] Wilson WH,[5] Pittaluga S,[1] Meltzer PS,[3] Staudt LM,[5] Emmert-Buck MR,[1] Jaffe ES[1]

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Mediastinal gray zone lymphoma (MGZL) is a newly recognized entity that demonstrates transitional morphologic and phenotypic features between classical Hodgkin's lymphoma, nodular sclerosis subtype (CHLNS) and primary mediastinal large B-cell lymphoma (PMBL). CHLNS and PMBL differ in morphology, immunophenotype, and therapeutic consequences. MGZLs present a challenge both to the pathologist and clinician, as the criteria to distinguish MGZL from CHLNS and PMBL are still imprecise, and the optimal treatment approach is as yet undetermined. Epigenetic changes have been implicated in the loss of the B-cell program in CHL, and might provide a basis for the immunophenotypic alterations seen in MGZL. Thus, we performed a large scale DNA methylation array of MGZL, CHLNS, PMBL as well as diffuse large B-cell lymphoma (DLBCL) to investigate the biological underpinnings of MGZL and how it corresponds to the two related entities CHLNS and PMBL and the less related entity DLBCL. Microdissection of tumor cells was performed to identify changes in the tumor cell population, and allow comparison with the background inflammatory and stromal milieu. Principal component analysis (PCA) demonstrated that MGZLs have a distinct epigenetic profile intermediate between CHLNS and PMBL but remarkably different from that of DLBCL. Analysis of common hypo- and hypermethylated CpG targets in MGZL, CHLNS, PMBL and DLBCL was performed. MGZL showed great overlap with CHLNS (49 common targets) and PMBL (50 common targets). In contrast, MGZL shared only two targets with DLBCL. Based on the epigenetic profiles we were able to establish class prediction models that could distinguish between MGZL, CHLNS and PMLBL with a final combined prediction of 100%. Pyrosequencing for selected CpG sites from different genes confirmed the high accuracy of the methylation results. MGZLs share several clinical and pathological features with CHLNS and PMBL. Our findings further underscore the close biological relationship between MGZL, CHLNS and PMBL, and ready distinction from DLBCL. However, MGZL has a distinct epigenetic identity that shares elements of both parent disorders. As the first biological study of MGZL, our results provide not only novel insights into MGZL pathogenesis, but also reveal potentially useful targets for MGZL diagnosis and future therapies.

P004

ABSENCE OF HLA-DM PREVENTS HLA CLASS II ANTIGEN PRESENTATION IN A SUBSET OF HODGKIN LYMPHOMA PATIENTS

Diepstra A, Xu C, Visser L, Kluiver J, Plattel W, Poppema S, van den Berg A

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Background. Cell surface HLA class II (sHLA-II) expression by Hodgkin Reed-Sternberg (HRS) cells predicts favourable outcome in classical

Hodgkin lymphoma (cHL) patients, indicating the presence of HLA class II restricted anti-tumor immune responses. These responses depend on proper presentation of immunogenic peptides in the antigen binding groove of HLA class II, which have to displace the class II associated invariant chain peptide (CLIP) during normal HLA class II processing. A defect in the loading of antigenic peptides would result in presentation of non-immunogenic CLIP in the context of sHLA-II. We investigated the antigen presenting capacity of sHLA-II molecules in cHL cell lines and patients. *Patients and methods.* Quantitative RT-PCR was used to determine expression levels of all major HLA class I and II genes in cHL cell lines L428, L591, L1236, HD-LM2 and KM-H2. The expression levels were compared to CD77+ tonsillar centroblasts. In addition, immunohistochemistry (IHC) was done to detect (cell surface) CLIP, HLA class II, HLA-DM and HLA-DO in cell lines and frozen tissue samples of 21 cHL patients with sHLA-II+ HRS cells. *Results.* By quantitative RT-PCR the L591 cell line showed expression of all major HLA class II genes comparable to centroblasts, while the other cHL cell lines had lower expression levels. By IHC all cell lines expressed sHLA-II, without expression of sCLIP, indicating proper presentation of antigenic peptides. Remarkably, 10 out of 21 sHLA-II+ patients showed a strong HRS sCLIP staining. This coincided with absence of the HLA class II accessory molecule HLA-DM that is essential for the exchange of CLIP with antigenic peptides. The HLA-DM inhibitor HLA-DO was not involved, showing no expression. *Conclusions.* Our results show that antigen presentation in the context of HLA class II can be disturbed not only by lack of sHLA-II expression, but also by specific down regulation of HLA-DM in cHL patients. Complete HLA-DM down regulation does not occur in cHL cell lines and is consistent with their ability to stimulate T lymphocyte proliferation in mixed lymphocyte reactions. Further studies are needed to evaluate HLA-DM and/or CLIP expression as a potential prognostic factor in cHL patients.

P005

THE ROLE OF BASELINE LEVELS OF INTERLEUKIN-6 AND HEPCIDIN FOR ANEMIA AT DIAGNOSIS AND DURING THERAPY IN HODGKIN LYMPHOMA

Hohaus S, Vannata B, Giachelia M, Massini G, Cuccaro A, Tisi MC, Criscuolo M, D'Alò F, Swinkels DW, Voso MT, Leone G

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Introduction. Approximately 40% of patients with Hodgkin lymphoma (HL) present with anemia at diagnosis, which is typically a mild normochromic, normocytic anemia of chronic disease seen in a wide variety of inflammatory states. We have recently shown that the IL-6-hepcidin axis is involved in mediating this anemia at HL diagnosis (Hohaus *et al.*, J Clin Oncol. 2010;28:2538-43). Our objective now was to study their potential predictive role in HL for changes of hemoglobin levels during the treatment. *Methods.* We studied 65 HL patients. Plasma samples at diagnosis were analyzed for levels of the cytokines IL-6, IL-10, and the chemokine TARC using ELISA techniques (R&D Diagnostics), while hepcidin levels were determined using a combination of weak cation exchange chromatography and time-of-flight mass spectrometry (TOF MS), as described previously (Swinkels *et al.*, PLOS ONE 2008; 3:e2706). Standard treatment of patients was ABVD (n=38), while young patients with advanced stage disease were treated with BEACOPP (dose-escalated)(n=24). *Results.* Hemoglobin levels were below 12 g/dL in 31 patients, and did not differ according to treatment regimen. Hemoglobin levels were lower in female patients, patients with age >45 years, in the presence of B-symptoms, stage IV disease and with a higher IPS score (>2). As expected, changes of haemoglobin levels during treatment strongly depended on the regiomen: Patients treated with BEACOPP regimen had a steeper decrease of haemoglobin levels in comparison to patients treated with ABVD (-1.07 g/dL per month versus -0.19 g/dL), were more likely to receive red blood cell (RBC) transfusions (42% vs 11%) and were more often treated with erythropoiesis-stimulating agents (ESA) (81% vs 7%)(all P<0.01). IL-6 levels correlated with haemoglobin levels, and also predicted for development of anemia necessitating therapy with ESAs and/or RBC transfusions during therapy of initially non-anemic patients (P=0.04). Hepcidin levels inversely correlated with haemoglobin values at diagnosis in anemic patients (r=-0.45, P=0.01), but did not predict for development of anemia during therapy. *Conclusion.* IL-6 levels at diagnosis were not only correlated with haemoglobin levels at diagnosis, but also predicted a decrease of haemoglobin levels during therapy.

P006

SEROPOSITIVITY FOR HUMAN CYTOMEGALOVIRUS IS ASSOCIATED WITH AN INCREASED RISK OF BOTH EBV-NEGATIVE AND EBV-POSITIVE CLASSICAL HODGKIN LYMPHOMA

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Classical Hodgkin Lymphoma (cHL) is associated with Epstein-Barr Virus (EBV) in a proportion of cases. Among adults, risk of EBV-associated cHL is associated with age and HLA-A genotype suggesting that cell mediated immunity to EBV plays a critical role in disease development. In CMV seropositive individuals much of the T-cell response is CMV-restricted (10-50% over 60 years of age) and EBV-specific responses are impaired. We therefore investigated the hypothesis that CMV infection increases risk of EBV-associated cHL, particularly among older adults. Serum samples from 549 cHL cases and 396 controls were analysed using the Abbot CMV IgG chemiluminescent microparticle immunoassay. CMV seropositivity was compared in: cHL cases versus controls; EBV-positive cHL cases versus controls; EBV-negative cHL cases versus controls; and EBV-positive cHL cases versus EBV-negative cHL cases using logistic regression. Overall, 51.1% of subjects were CMV seropositive and seropositivity increased with age. After adjusting for effects of age and sex, cHL was independently associated with CMV seropositivity (odds ratio (OR) cases versus controls=1.45, 95% confidence interval (CI) 1.08-1.95.) Significant differences were observed for both EBV-associated cHL (OR EBV-positive cases versus controls=1.59 95% CI 1.06-2.46) and EBV-negative cHL (OR 1.41, 95% CI 1.02-1.95.) There was no significant difference in CMV seropositivity between EBV-positive and negative cHL cases. Following stratification by age, case:control differences were significant only in adults >50 years (OR 1.76, 95% CI 1.09- 2.49); ORs were greatest for EBV-positive cHL cases versus controls (OR 2.37, 95% CI 1.17-4.82.) The data support the hypothesis that reduced immune surveillance due to CMV infection leads to an increased risk of cHL, particularly in older adults; however, this increased risk is not restricted to EBV-associated cHL. Results are currently being validated in an independent case-control sample.

P007

DEREPRESSION OF AN ENDOGENOUS LONG TERMINAL REPEAT ACTIVATES THE CSF1R PROTO-ONCOGENE IN HODGKIN LYMPHOMA

Lamprecht B,[1,2] Korden W,[3] Kreher S,[1,2] Kumar R,[4] Hummel M,[5] Lenze D,[5] Köchert K,[1,2] Amine Bouhlel M,[3] Richter J,[6] Soler E,[7] Stadhouders R,[7] Jöhrens K,[5] Wurster KD,[1,2] Callen DF,[4] Harte MF,[8] Giefing M,[6] Barlow R,[3] Stein H,[5] Anagnostopoulos I,[5] Janz M,[1,2] Cockerill PN,[3] Siebert R,[6] Dörken B,[1,2] Bonifer C,[3] Mathas S[1,2]

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The aim of this study was to analyze mechanisms and consequences of lineage-inappropriate gene expression in classical Hodgkin Lymphoma (HL). Hodgkin-/Reed-Sternberg (HRS) cells, that usually originate from mature B cells, have largely lost expression of B cell-specific genes, including expression of the B cell receptor gene (BCR), and instead have acquired features of other lineages. The upregulation of such non-B genes in HRS cells might provide alternative growth and survival signaling for HRS cells. As a candidate for a B lineage-inappropriate gene we identified the myeloid-specific proto-oncogene colony-stimulating factor 1 receptor (CSF1R) and its ligand CSF-1 in HRS cell lines and primary HRS cells thereby suggesting an autocrine loop. We showed that malignant HRS cells of HL depend on signaling through the CSF1R. Inhibiting CSF1R activity induced growth arrest and cell death of HRS cell lines. Furthermore, we demonstrated that CSF1R transcription in HRS cells does not initiate at its canonical myeloid promoter, but at an aberrantly acti-

vated endogenous LTR of the THE1 family (THE1B). We could show that the THE1B-LTR is able to drive transcription and we detected THE1B CSF1R transcripts not only in HRS cell lines but also in Hodgkin Lymphoma affected lymph node samples. Given the fact that LTR regions are epigenetically silenced in healthy cells we next investigated mechanisms behind THE1B-LTR derepression in HL. We searched for factors that were responsible for epigenetic chromatin modifications and found a loss of CBFA2T3 protein in HRS cells. RNA interference mediated downregulation of CBFA2T3 in non-Hodgkin B cells resulted in noncanonical CSF1R transcripts derived from the THE1B-LTR. Finally, we investigated if derepression of LTRs was a common phenomenon in HRS cells and could indeed identify widespread expression of THE1-LTR derived transcripts in HRS cell lines. Our data suggests that the upregulation of non-B lineage genes, which are normally silenced in B cells, might provide alternative survival pathways following loss of BCR activity in HRS cells. Furthermore, our data show for the first time that LTR derepression leads to upregulation of a proto-oncogene in a human malignancy, a finding, which might have diagnostic, prognostic and therapeutic implications.

P008

MASS-SPECTROMETRIC CELL SURFACE PROTEIN PHENOTYPING OF HODGKIN LYMPHOMA

Hofmann A,[1-3] Thiesler T,[5] Gerrits B,[4] Behnke S,[5] Omasits U,[1] Bausch-Fluck D,[1,3] Bock T,[1,3] Aebersold R,[1,6] Moch H,[5] Tinguely M,[5*] Wollscheid B[1,3*]

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Background. The cell surface phenotype of classical Hodgkin lymphoma (cHL) and non-Hodgkin lymphoma(NHL) cells is critically important for diagnosis and therapy. Cell surface proteins are key mediators for signal transduction and promising targets for the distinction of different lymphoma subtypes and subsequent therapeutic intervention using small molecule or antibody-based approaches. Comprehensive cell surface protein marker expression analysis towards the identification of the cHL and NHL surfaceome is currently hampered by the limited availability of suitable antibodies for flow cytometry analysis/immunohistochemistry. Here we present the mass-spectrometry based quantitative analysis of the cHL and NHL surfaceome. *Methods.* We used version 2.0 of the recently published Cell Surface Capturing (CSC) technology1 which enables the discovery-driven phenotyping of cells without antibodies. The surfaceome of eight different cHL and B-NHL cell lines was comprehensively investigated qualitatively and quantitatively. Identified proteins were relatively quantified inbetween the samples by spectral-counting. Differentially expressed candidate protein markers were tested by IHC on an in-house developed TMA containing cHL, FL, MZL, and DLBCL of 126 patients. *Results.* The CSC technology v2.0 enabled the parallel discovery of more than 1000 bona fide membrane proteins, including 178CD molecules in cHL and B-NHL cell lines. 459 of the identified membrane proteins were only identified in one lymphoma group. Functional protein groups showed disease specific characteristics. Hierarchical cluster analysis of protein identifications separated cHL from B-NHL cell lines and even B- from T-cell derived cHL cell lines. Among the panel of classification markers tested on primary tissues, three markers were identified and qualified as promising supplementary markers. These markers complement the current clinical cHL panel and can improve the differentiation of cHL from overlap B-cell lymphomas. *Conclusion.* The CSC technology v2.0 allowed for the extensive qualitative and quantitative analysis of the surfaceome of cHL in comparison to NHL. CSC analysis revealed a Systems Biology-type of perspective of the cHL and NHL surfaceome which can now be used to model cellular interactions with the cancer microenvironment. We extracted from the cHL surfaceome three diagnostic candidate biomarkers for further subclassification of cHL which need to be further validated in larger patient cohorts in ongoing prospective studies.

P009

RECURRENT DELETIONS BUT NO MUTATIONS OF NOVEL TSG CANDIDATES IN CHL

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By delineating homozygous deletions using high resolution array-CGH to classical Hodgkin lymphoma cell lines (cHL) we recently identified several novel tumor suppressor gene candidates (CD70, CHD2, CYBB, GNG7, SEPT9, TNFSF9). In order to investigate if these genes are recurrently deleted in primary tissue we analyzed a cohort of 21 cryo-sections of lymph-nodes of cHL on single cell level using the FICTION technique. Subsequently, we sequenced the coding regions of genes with the highest deletion incidence in seven cHL cell lines. The FICTION approach combines CD30$^+$ immunostaining to detect single. Hodgkin and Reed-Sternberg cells with fluorescent in situ hybridization (FISH). BAC clone targeting the analyzed genes were used as FISH probes together with commercial centromere probes as a reference. The copy number of the analyzed genes was calculated (i) in comparison to the number of centromere signals in a particular tumor cell (ii) in comparison to the ploidy of the case. The ploidy of each case was defined as the median signal number of the various centromere probes used. In each hybridization 10 to 40 CD30$^+$ tumor cells were evaluated by two independent observers. A deletion was scored if at least 30% of the cells showed lower number of signals for the gene specific probe than for centromere probe and the ploidy level. Gene copy number losses in the primary samples were identified with the following frequencies: CYBB 6/18 (33%); CHD2 5/19 (26%); GNG7 2/18 (11%); TNFSF9 2/18 (11%); CD70 2/18 (11%); SEPT9 0/17 (0%). No homozygous deletions were identified in the primary cases. Highly recurrent losses and expression profiling allowed the selection of CYBB, CHD2 and GNG7 for subsequent mutation analysis. All coding exons of these genes have been sequenced in seven cHL cell lines. No mutations were identified. In summary, this study shows that CYBB (cytochrome b-245, part of the NADPH - Nox2 oxydase) a key factor in the intrinsic cell death pathway and CHD2 (chromodomain helicase DNA binding protein 2) a chromatin condensation and gene expression regulator - are frequently deleted but not mutated in cHL.

P010

EFFECTS OF RECEPTOR TYROSINE KINASE INHIBITORS ON HODGKIN LYMPHOMA DERIVED CELL LINES

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Receptor tyrosine kinases (RTKs) are involved in the regulation of most cellular processes and often aberrantly activated in tumours. Several RTKs, such as PDGFRA, TRKA/B, RON, DDR2 and EPHB1, are aberrantly expressed in Hodgkin-Reed/Sternberg (HRS) cells of classical Hodgkin lymphoma (HL) and activated by auto- and paracrine mechanisms.[1,2] We therefore analysed the effect of receptor tyrosine kinase inhibitors on HRS derived cell lines. In an initial screen nine RTK inhibitors already approved or in advanced stages of clinical trials for the treatment of other cancers (Dasatinib, Erlotinib, Gefitinib, Lapatinib, Lestaurtinib, Sorafenib, Sunitinib, Vandetanib, Vatalanib) were tested. Lestaurtinib and Sorafenib showed an anti-proliferative effect in three of five HRS cell lines at concentrations achievable as plasma concentrations in patients and were thus analysed in more detail. Although both inhibitors diminished cell growth of KM-H2, L-428 and L-1236 cells at optimal growth conditions in a concentration dependent manner, the effect was mainly cytostatic as no apoptotic response could be detected by Western blotting for activated Caspase-3 or FACS analysis after Annexin V staining. By phospho-RTK-specific immunoblotting RON was newly identified as a target of both drugs and PDGFRA as a new target of Lestaurtinib. The inhibitory effect of Sorafenib on PDGFRA and RAF1 and of Lestaurtinib on JAK2 could be confirmed.

Several constituents of JAK2/STAT, RAS/RAF/MAPK and PI3K pathways were deactivated in response to RTK inhibition in Western blot analysis. The combination of Lestaurtinib with other RTK inhibitors (Lapatinib, Sorafenib, Sunitinib) had at least additive cytostatic effects but could also not induce cell death. Combining Lestaurtinib and Sorafenib with Doxorubicin or Vinblastine, chemotherapeutica typically used in HL therapy, had only minor additional effects on cell growth inhibition. In summary, Lestaurtinib and Sorafenib inhibit several tyrosine kinases in HRS cell lines with cytostatic effects at concentrations achievable in patients and enhance the effects of Doxorubicin and Vinblastine.

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P011

EXPRESSION AND FUNCTION OF TOLL LIKE RECEPTORS TLR4, TLR7 AND TLR9 IN CLASSICAL HODGKIN LYMPHOMA

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Background. Toll like receptors (TLRs) have been implicated in the pathogenesis of many hematological malignancies by modulating the immune response and by providing tumor cell survival signals. In classical Hodgkin lymphoma (cHL), which is characterized by an extensive reactive infiltrate, the role of TLRs has not been studied yet. *Methods.* We tested the expression of TLR4, TLR7 and TLR9 by immunohistochemistry on paraffin sections and expression of TLR2 on frozen sections of 19 patients diagnosed with classical Hodgkin lymphoma. The expression of FoxP3 and IL17 was used to count regulatory T cells and Th17 cells respectively. Ligation of TLRs on cHL cell lines was performed to study the functionality of the TLRs with respect to induction of cytokine production, cell growth, and phosphorylation of downstream targets. *Results.* TLR4, TLR7 and TLR9 were expressed in Hodgkin Reed-Sternberg (HRS) cells in a variable percentage of cHL cases, whereas TLR2 was consistently negative. In contrast to their pathogenic role in other malignancies, we observed only minor effects upon ligation of TLR4, TLR7 and TLR9 in cHL cell lines. There was no correlation of TLR expression with presence of regulatory T cells or Th17 cells and also not with expression of HLA class I and class II in HRS cells in patient tissue samples. Ligation of TLR4, TLR7 and TLR9 in cHL cell lines did not induce production of IL-1, IL-6 or IL-10 and induced only minor effects on cell growth. The most pronounced effect on cell growth was observed upon ligation of TLR7 in KMH2 cells, which was associated with upregulation of p-JNK1/2 and p-Erk1/2. Triggering of TLR9 suppressed cell growth in some cHL cell lines. *Conclusion.* We found expression of TLR4, TLR7 and TLR9 in HRS cells, whereas TLR2 was not expressed. The responsiveness to ligation is limited with no effect on cytokine production and only a moderate effect on cell growth in cHL cell lines. In cHL tissue no association of TLR expression was observed with presence of regulatory T and Th17 cells or expression of HLA. These findings indicate a hyporesponsive state of these three TLRs in cHL.

P012

FUNCTIONALITY OF THE HLA-A*02 ALLELE IN EPSTEIN BARR VIRUS POSITIVE CLASSICAL HODGKIN LYMPHOMA

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Background. Based on previous studies it has become evident that presentation of EBV derived peptides in the context of HLA-A plays a crucial role in the pathogenesis of EBV$^+$ cHL. The HLA-A*02 allele is associated with reduced risk, whereas the HLA-A*01 allele is associated with an increased risk of developing EBV$^+$ HL. The HLA-A*02 allele has a high affinity for EBV antigenic peptides derived from LMP1 or LMP2, whereas the HLA-A*01 allele is not able to present antigenic peptides from these proteins. We showed that 27% of the HLA-A*02 positive HL patients are EBV$^+$. We now analyzed the functionality of the HLA-A*02 allele in HLA-A*02+ / EBV$^+$ cHL. *Methods.* We collected frozen tissue of 12 HLA-A*02+ / EBV$^+$ cHL patients. Immunohistochemistry was performed to determine the HRS cell surface expression of HLA-A*02 and HLA class I. Point mutation analysis in the HLA-A peptide binding region (exons 2 and 3) was performed on laser microdissected HRS cells by a nested PCR followed by direct sequencing. Primers were designed to preferentially amplify the HLA-A*02 allele. *Results.* Membranous HLA B/C expression was observed in 6 of 12 patients. Five of these HLA B/C positive cases also showed membranous HLA-A*02 expression, whereas the pattern in the sixth was heterogeneous. The six HLA B/C negative patients were also negative for HLA-A*02. For 4 patients (two HLA-A*02 negative, one positive and one heterogeneous) amplification of the HLA-A exon 2 and 3 region was performed successfully. Sequencing of at least two independent HLA-A*02 PCR products revealed no mutations. Mutation analysis of the remaining cases is still ongoing. *Conclusions.* Six of the 12 EBV$^+$ cHL patients lacked HLA class I expression based on loss of both HLA B/C and HLA-A*02 on HRS cell membrane. This suggests that these patients lack an effective CTL response against the EBV$^+$ HRS cells. Presence of HLA-A*02 membranous expression in the other six cases suggests that mechanisms other than downregulation of surface expression of HLA class-I and HLA-A*02 are involved.

P013

MECHANISMS OF ABERRANT GATA-3 EXPRESSION IN CLASSICAL HODGKIN LYMPHOMA AND ITS CONSEQUENCES FOR THE CYTOKINE PROFILE OF HODGKIN AND REED/STERNBERG CELLS

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The transcription factor network in Hodgkin lymphoma (HL) represents a unique composition of proteins found in no other hematopoietic cell. Among these factors, an aberrant expression of the T cell transcription factor GATA-3 is observed in the B cell-derived Hodgkin and Reed/Sternberg (HRS) tumor cells. In this work, we elucidated the regulation and function of this factor in HL. We demonstrate binding of NFkB and Notch-1, two factors with deregulated activity in HL, to GATA-3 promoter elements. Interference with NFkB and Notch-1 activity led to decreased GATA-3 expression, indicating a dependency of deregulated GATA-3 expression on these transcription factors. Downregulation of GATA-3 in HL cell lines demonstrated its role in the regulation of IL-5, IL-13, STAT-4 and further genes. A correlation between GATA-3 and IL-13 expression was confirmed for HRS cells in primary HL tissues. However, unlike IL-13 reduction downregulation of GATA-3 did not lead to apoptosis induction in HL cell lines. Thus, GATA-3 shapes the cytokine expression and signalling that is typical for HL. Conclusively, aberrant GATA-3 expression in HRS cells is stimulated by the deregulated constitutive activity of NFkB and Notch-1, indicating a complex network of deregulated transcription factors in these cells. GATA-3 activity significantly contributes to the typical cytokine secretion of and signalling in HRS cells, which presumably plays an essential role in HL pathogenesis.

P014

EXPRESSION OF THE C-MET ONCOGENE CORRELATES WITH FAVORABLE PROGRESSION FREE SURVIVAL IN CLASSICAL HODGKIN LYMPHOMA

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Background. The HGF/Met signaling pathway regulates a variety of biological processes, including proliferation, survival and migration. Deregulated Met activation has been implicated in the pathogenesis and prognosis of many human cancers, such as diffuse large B cell lymphoma, bladder cancer, breast cancer, colorectal cancer and ovarian cancer. Expression of c-Met has been reported in HL, but no prognostic studies or functional

data have been reported. *Methods.* We studied the prognostic significance of Met expression by immunohistochemistry on paraffin sections of classical Hodgkin lymphoma (cHL) patients from two independent patient cohorts. Functional studies were performed on HL cell line L428 that showed high Met levels and no HGF expression. The effect of stimulation by HGF and inhibition by Met kinase inhibitor SU11274 was investigated on Western blot, cell proliferation and cell cycle progression. *Results.* Expression of Met was detected in Hodgkin Reed-Sternberg (HRS) cells in 52% (79/152) of primary cHL tissue samples and expression of its ligand, hepatocyte growth factor (HGF), was detected in HRS cells in 8% (10/120) of the cHL patients. A variable percentage of infiltrating cells stained positive for HGF, supporting a predominant paracrine activation route. In contrast to its adverse prognostic impact in other cancers, high Met expression significantly correlated with favorable 5 year progression free survival in both patient cohorts. To further investigate these unexpected findings we studied the Met/HGF signaling pathway in the L428 cHL cell line. The levels of phosphorylated Met, Akt, and Erk1/2 were upregulated upon HGF stimulation and this induction could be blocked by inhibiting Met activation with SU11274. Activation with HGF did not effect cell growth, while SU11274 alone suppressed cell growth. SU11274, as well as inhibitors of PI3K, MEK1/2 and Erk1/2 (downstream targets of the HGF/Met signaling pathway), induced G2/M cycle arrest. *Conclusion.* Expression of Met in tumor cells was observed in 52% of cHL patients. Although functional studies show a role of the HGF/Met signaling pathway in the regulation of cell cycle progression in L428, expression of Met in patients correlated with favorable prognosis in two independent cohorts.

P015

NO EVIDENCE OF THE NOVEL RETROVIRUS XMRV IN HODGKIN LYMPHOMA AND OTHER LYMPHOID MALIGNANCIES

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A novel retrovirus, xenotropic murine leukaemia virus-related virus (XMRV), has been detected in prostatic cancer samples and in peripheral blood mononuclear cells (PBMCs) from patients with chronic fatigue syndrome. In addition, the virus has been identified in PBMCs from healthy controls. These data suggest that XMRV is circulating in the human population. XMRV is closely related to murine leukaemia viruses, which cause lymphoid malignancies in mice. The aim of the current study was to determine whether XMRV is associated with Hodgkin lymphoma (HL) and other human lymphoid malignancies. Although epidemiological data suggest involvement of an infectious agent in Epstein-Barr virus (EBV)-negative HL, no potential agents have been detected as yet. Using three specific and sensitive, quantitative PCR assays to the gag, pol and env genes of XMRV, we screened DNA samples from 368 patients with lymphoid malignancies. These included samples from patients with: classical HL (n=82); nodular lymphocyte predominant HL (n=31); common acute lymphoblastic leukaemia (n=52); follicular lymphoma (n=59); and diffuse large B-cell lymphoma (n=58). Samples from 140 patients with benign lymphadenopathy or other malignant disease were included as controls. The integrity of all DNA samples was confirmed using a -globin TaqMan® assay. XMRV was not detected in any of our samples using the three specific XMRV assays. The assays were sensitive enough to consistently detect 16 copies of the virus in 1 ug of background DNA. We therefore found no evidence that XMRV is directly involved in the pathogenesis of common types of human lymphoid malignancy, including Hodgkin lymphoma. Further studies are required to resolve inconsistencies in the literature regarding XMRV prevalence and pathological significance. The search for an infectious agent in EBV-negative HL continues.

P016

METAPHASE FISH ANALYSIS IN PRIMARY MEDIASTINAL B CELL LYMPHOMA AND HODGKIN LYMPHOMA

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Background. Whereas interphase FISH results have been often reported in primary mediastinal B cell lymphoma (PMBCL) and classical Hodgkin lymphoma (CHL), studies reporting conventional cytogenetics or metaphase FISH results remain rare. *Materials and methods.* Probes targeting P16, JAK2, IGH, REL, BCL6 and PAX5 have been used on metaphases from 11 PMBCL and 26 CHL patients. The P16 (FITC) and JAK2 (spectrum orange) probes were hybridized together, all other probes were subsequently hybridized on the same metaphasesFor PMBCL: On conventional cytogenetics analysis, 9/11 karyotypes were abnormal. Those were mainly in the diploid range (46-56 chromosomes for ten patients, 100 chromosomes for 1 patient). *Results.* For Hodgkin lymphoma, all 26 karyotypes were abnormal, in the diploid range (46-53) for 9 of 26 patients, triploid or over for 17 of 26 patients, 2 of which had both a diploid and a duplicated component. FISH analysis: for PMBCL 9 of 11 patients had an abnormal FISH pattern. The most frequent abnormalities were a gain of all/most probes targeting the 9p region (8/11 patients, one with a gain of P16 and JAK2 but not of PAX5), and a gain of REL, present in 6/11 patients. Two patients had a normal FISH pattern, of whom one with an abnormal karyotype – add(9)(p24) – was normal for all tested probes and one with both a normal karyotype and a normal FISH analysis). Another discrepancy corresponded to a normal conventional karyotype with a double gain of P16, JAK2 and PAX5 upon FISH analysis. Rearrangements of both IgH and BCL6 genes were absent in this series. Regarding classical Hodgkin lymphoma, the number of chromosome gains was in accordance with the chromosome number, with a low intraclonal variation. No structural rearrangement involving the IgH or BCL6 gene could be detected. A simultaneous high level amplification of both BCL6 and PAX5 was present in one patient. *Conclusion.* Those results do not differ from previously reported results obtained by interphase FISH. The chromosome number of IGH and BCL6 signals remains the more reliable way to discriminate hyperdiploid CHL from PMBCL.

P017

ACTIVITY OF SGN-35 IN PRECLINICAL MODELS OF COMBINATION THERAPY AND RELAPSE PREVENTION

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SGN-35 is an antibody-drug conjugate (ADC) consisting of the potent antitubulin agent monomethyl auristatin E (MMAE) conjugated to an anti-CD30 antibody. SGN-35 selectively induces apoptosis in CD30+ cells by binding, internalizing, and releasing MMAE. CD30 is expressed on Hodgkin Reed-Sternberg cells and several types of T-cell lymphoma but has limited expression on normal tissues. SGN-35 is being tested in multiple clinical trials including a pivotal trial for relapsed/refractory Hodgkin lymphoma (HL) and a phase II trial for systemic anaplastic large cell lymphoma (ALCL). We previously reported that SGN-35 combined with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) or with gemcitabine had improved antitumor activity compared to chemotherapy alone or to SGN-35 monotherapy in a preclinical HL xenograft model. We have extended these studies to evaluate SGN-35 in combination with the histone deacetylase inhibitors (HDACi) panobinostat and vorinostat and with the mTOR inhibitors (mTORi) temsirolimus and sirolimus. SGN-35 and temsirolimus had synergistic cytotoxic activity *in vitro*.

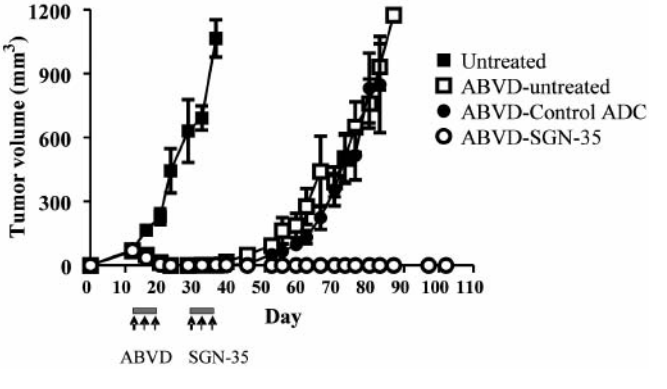

Figure 1. SGN-35 prevents tumor relapse post ABVD treatment in the L540cy Hodgkin lymphoma xenograft model.

At the ED50 values, combination indices of 0.76 and 0.45 indicating moderate synergism and synergism were obtained from HL L540cy and ALCL Karpas 299 cell lines, respectively. The effects of SGN-35 with HDACi were additive. *In vivo* studies of SGN-35 in combination with HDACi and mTORi are ongoing, results to be presented. SGN-35 was further tested in a preclinical model for its ability to prevent relapse of tumor growth after chemotherapy. Mice bearing L540cy tumors were treated with ABVD (over 12 days) until the tumors were no longer palpable. Approximately one week later, in the absence of measureable disease, mice were randomized and left untreated, or dosed three times (every 4 days) with SGN-35 or a non-binding control ADC (Figure 1). Whereas L540cy tumors ultimately re-grew in 6 of 7 of the untreated or control ADC-treated mice, animals treated with SGN-35 remained free of palpable tumors through the end of the study. These data demonstrate the potential of SGN-35 to prevent recurrence of residual disease. A phase III trial (AETHERA trial (ADC Empowered Trial for Hodgkin to Evaluate Progression after ASCT)) is ongoing for patients at high risk of residual Hodgkin lymphoma following autologous stem cell transplant.

P018

PROSPECTIVE ANALYSIS OF PLASMA LEVELS OF THYMUS AND ACTIVATION REGULATED CHEMOKINE (TARC) IN PRIMARY AND RELAPSED CLASSICAL HODGKIN LYMPHOMA PATIENTS

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Introduction. Thymus and Activation Regulated Chemokine (TARC) is highly expressed by the tumor cells in about 90% of classical Hodgkin lymphoma (cHL) patients. This chemokine is released in the circulation and may serve as a cHL specific biomarker. Previous reports showed high serum levels of TARC before start of treatment and a significant decrease in serum TARC levels after treatment. We aimed to correlate plasma TARC levels with metabolic response to chemotherapy as determined by FDG-PET imaging. *Patients and methods.* Patients with newly diagnosed or relapsed cHL in the University Medical Center Groningen were included from 2005 until 2009. TARC expression of HRS cells was evaluated by immunohistochemistry (IHC) on tissue samples at diagnosis. TARC levels in plasma collected before start of treatment, at mid-treatment FDG-PET evaluation and at completion of treatment were evaluated by ELISA. Patients were treated according to clinical trial (EORTC) or hospital protocols. *Results.* Of the 63 included primary cHL patients, median age was 33 years (range 16-80). IHC results showed TARC expression in 95% of the patients. Pre-treatment plasma TARC levels in stage II-IV disease were significantly higher compared to stage I disease (P=.002) and patients with bulky disease had significantly higher TARC values compared to patients without bulky disease (P=.04). TARC values were significantly decreased mid-treatment and after treatment (P<.0001). Thirteen patients had a positive mid-treatment FDG-PET scan. Two of those patients had significantly elevated mid-treatment TARC levels and failed first line treatment. Eleven patients had normal mid-treatment TARC levels and nine of them became FDG-PET negative at end of treatment. After treatment completion, high plasma TARC values were observed in three out of 5 FDG-PET positive patients. All eight relapsed patients had significantly elevated pre-treatment plasma TARC levels. *Conclusion.* Plasma TARC levels correlate with tumor burden and partially with response to therapy as measured by FDG-PET imaging in cHL. At time of relapse, plasma TARC levels were (re-)elevated. Evaluation of TARC dynamics in a larger study with a higher event rate is needed to establish the exact clinical value of serial plasma TARC monitoring in cHL.

P019

AN INVESTIGATION OF THE EBV LATENT MEMBRANE PROTEIN 2 IN HUMAN GERMINAL CENTRE B CELLS

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Although previous studies have suggested that the latent membrane protein 2 (LMP2) could be important for the EBV-induced transformation of germinal centre (GC) B cells, the contribution of this viral gene to the pathogenesis of EBV-associated lymphomas, such as Hodgkin's lymphoma (HL), remains unknown. It has been shown previously in cell lines and in murine models that LMP2a can mimic B cell receptor (BCR) functions, but so far the effects of LMP2a and BCR signalling have not been investigated in primary human GC B cells, the putative progenitor cells of cHL. We developed a transfection based method that enables the study of gene expression and signalling mediated by LMP2a in purified GC B cells. Consistent with previous reports on cell lines and in transgenic mice, we observed that LMP2A induced a global down-regulation of B cell lineage genes, including B cell signalling components, as well as affecting the expression of genes involved in antigen presentation. Many of the LMP2 target genes were also modulated in GC B cells by BCR cross-linking, demonstrating the overlapping functions of LMP2a and BCR in this cellular context. Remarkably, B cell specific genes regulated by LMP2a showed an overlap with LMP1 targets in GC B cells. These observations support the hypothesis that EBV latent proteins contribute to transformation by bypassing critical checkpoints in B cell development. It also emphasises the importance of using primary human GC B cells when investigating the contribution of viral and cellular genes to the pathogenesis of GC-derived lymphomas.

P020

IS WT-1 A NEW PRO-ANGIOGENIC MARKER IN HODGKIN LYMPHOMA?

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Introduction. WT-1 (Wilms' tumor gene 1) is a transcription factor first found in Wilms' tumor of the kidney, where it acts as a tumor suppressor gene. It has a role in in-vitro regulation of endothelial cell proliferation and migration. Recently, WT-1 was found in hematological malignancies. WT-1 serves as a marker for prognosis and minimal residual disease in acute leukemia. There is no data concerning the involvement of WT-1 in angiogenesis in lymphomas and Hodgkin's lymphomas. The aim of this study was to explore the involvement of WT-1 in Hodgkin lymphoma. *Methods.* The expression of WT-1, NEUROPILIN 1 and VEGF was tested by immunohistochemestry in lymph nodes biopsies of 20 Hodgkin patients and 7 reactive lymph nodes. The extent of angiogenesis was tested by counting the average number of vessels per high power field. *Results.* WT-1 was expressed in endothelial cells, in 95% of the malignant lymph nodes. The average of WT-1 expression scale was higher in malignant lymph nodes than in reactive nodes. NP-1 was expressed in 92% of the endothelial cells in the malignant lymph nodes, and in none of the reactive lymph nodes. Endothelial cells that were NP-1 positive were also WT-1 positive. VEGF was expressed only in 71% of the malignant nodes. In the reactive lymph nodes VEGF was stained in higher intensity compared to the malignant lymph nodes. However, the angiogenic extent was higher in the malignant lymph nodes. We found a positive correlation between WT-1 expression scale and the ANGIOGENESIS scale (0.53) which was statistically significant (P<0.05). As the number of vessels increases, the expression of WT1 is more intense. *Conclusions.* We found, for the first time, that WT-1 and NP-1 are expressed in endothelial cells in Hodgkin lymphoma. The extent of angiogenesis was higher in Hodgkin than in the reactive lymph nodes, although VEGF expression was lower. This could be the result of higher NP-1 expression, which is known to aggravate the biological effects of VEGF. Positive correlation between angiogenesis and WT-1 expression was demonstrated. Further studies would reveal if WT1 could serve as a clinical marker for prognosis in Hodgkin lymphoma.

P021

ANALYSIS OF CHROMOSOMAL TRANSLOCATIONS INVOLVING IMMUNOGLOBULIN GENES OF PRIMARY HODGKIN AND REED-STERNBERG CELLS

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In most mature B cell non-Hodgkin lymphomas characteristic chromosomal translocations involving the immunoglobulin (Ig) genes are detected which play a major role in the pathogenesis of these lymphomas. As

Hodgkin and Reed-Sternberg (HRS) cells of classical Hodgkin lymphoma also originate from B cells, we decided to analyse isolated HRS cells for chromosomal translocations involving the Ig genes. In FISH/FICTION analysis it was previously shown that such chromosomal translocations involving the Ig loci occur in about 20% of primary cases. In order to further characterize the translocations, an LDI (long distance inverse) PCR strategy to detect chromosomal translocations involving the Ig heavy chain locus has been adapted to small cells amounts. To further handle the problem of the high number of different LDI-PCRs to perform and the scarcity of the HRS cells in the tumour tissue, a whole genome amplification (WGA) starting with 500 microdissected HRS cells is currently being established for the use prior to LDI-PCR. LDI-PCR studies on Hodgkin lymphoma cell lines already identified a complex translocation involving chromosomes 10 and 14 in L1236. The subsequent analysis could assign the breakpoints as switch- /10q11 and 10q11/switch- resulting from an incorrect class-switch-recombination. So far, it was not possible to identify a candidate gene encoding for a protein or miRNA which dysregulation contributed to the development of this Hodgkin lymphoma. The WGA approach established here will also be very useful for future experiments, such as mutation status analysis of certain genes, as it hugely reduces the number of cells to microdissect.

P022

HUMAN LEUKOCYTE ANTIGEN GENES ARE ASSOCIATED WITH RISK OF EBV-NEGATIVE HODGKIN LYMPHOMA

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Human leukocyte antigen (HLA) A alleles are strongly associated with EBV-associated classical Hodgkin lymphoma (cHL). HLA-A*0101 alleles are associated with increased risk of cHL while HLA-A*0201 alleles are associated with protection. To further explore associations between HLA and both EBV-associated and non-associated cHL, we have extended these analyses to HLA class I A and B loci. HLA typing was performed on 300 cHL cases and 335 controls using a PCR sequence specific oligonucleotide assay. Four comparisons were performed: cases versus controls; EBV-associated cases versus controls; non EBV-associated cases versus controls; and EBV-associated cases versus non EBV-associated cases. Logistic regression was used to estimate odds ratios (ORs) with 95% confidence intervals (CIs) and analyses were adjusted for the effects of age, sex, number of HLA-A*01 and A*02 alleles, and history of infectious mononucleosis. We hypothesised that HLA-B*07 and B*08 would decrease risk of EBV-associated cHL since both are known to present EBV-specific peptides. Following adjustment for the effect of HLA-A alleles we found no effect of HLA-B*08, which is in linkage dysequilibrium with HLA-A*01. Numbers of HLA-B*07 carriers differed significantly between EBV-associated and non-associated cases (dominant effect, OR EBV-associated cHL=0.38, CI 0.18-0.78) and the effect was dominant. Case-control comparisons revealed that HLA-B*07 was a risk allele for non-EBV-associated cHL (OR=2.24, CI 1.51-3.33) but neither risk nor protective for EBV-associated cHL (OR=0.73, CI 0.37-1.43). In addition, these analyses showed a significant interaction between HLA-A*01 and B*07 alleles. Taken together with our previous data, these findings indicate that risk of both EBV-associated and non-associated cHL is associated with markers in the HLA region.

P023

INTERACTION OF HRS CELLS WITH COLLAGEN CONTRIBUTES TO THE PATHOGENESIS OF HODGKIN'S LYMPHOMA BY ACTIVATING THE RECEPTOR TYROSINE KINASE, DISCOIDIN DOMAIN RECEPTOR 1

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The receptor tyrosine kinase, discoidin domain receptor 1 (DDR1), is unusual among RTKs as it responds to activated collagen rather than soluble growth factors. Given the abundance of collagen within the microenvironment of classical Hodgkin's lymphoma (cHL) we have asked if collagen induced activation of DDR1 is involved in the pathogenesis of cHL. We show that when compared to germinal centre B cells, the presumed progenitors of HL, DDR1 is overexpressed in Hodgkin Reed-Sternberg (HRS) cells in most cases. Furthermore, we observed that DDR1 overexpression was significantly more common in cases of nodular sclerosis disease where DDR1 expressing HRS cells were intimately associated with type IV collagen positive blood vessels. Whilst the majority of HL derived cell lines displayed evidence of DDR1 overexpression, in contrast the activation of DDR1 was variable between the cell lines. Thus, in some cell lines, DDR1 was constitutively activated, whereas in others DDR1 phosphorylation was strictly dependent upon stimulation of the cells with either type I or with type IV collagen. Analysis of global gene expression following the knockdown of DDR1 suggests a potentially oncogenic function for DDR1 in HRS cells. Our observation that DDR1 activation is mediated through the interaction of HRS cells with collagen identifies a hitherto unrecognised role for collagen in the pathogenesis of cHL.

P024

THE HEDGEHOG TRANSCRIPTION FACTOR, GLIOMA ASSOCIATED ONCOGENE HOMOLOGUE 3 (GLI3), IS HIGHLY EXPRESSED IN HODGKIN AND REED-STERNBERG CELLS OF CLASSICAL HODGKIN LYMPHOMA

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The Hedgehog (HH) signaling pathway has been shown to play a pathogenic role in diffuse large B-cell lymphoma (DLBCL) and anaplastic large cell lymphoma (ALCL), but has not been evaluated in classical Hodgkin lymphoma (CHL). We investigated the expression of HH related molecules including HH ligands, the transmembrane receptor smoothened (SMO) and the transcriptional effectors GLI1, GLI2 and GLI3, in 39 CHL patient samples and 4 CHL cell lines. Western blotting of CHL cell lines showed expression of the precursor and full length forms of HH ligands as well as all three GLI transcription factors. Real time reverse-transcriptase qPCR analysis of CHL cell lines confirmed the consistently elevated expression of GLI3 and variable expression of HH ligands, SMO, GLI1 and GLI2. By immunohistochemistry, HH, GLI1 and GLI2 proteins were weakly expressed at relatively low levels in a subset of CHL tumors. In contrast, GLI3 was uniformly and strongly expressed in the nuclei of virtually all tumor cells in CHL tumors. We also analyzed GLI3 protein expression by immunohistochemistry in 230 lymphomas including B- and T-cell non-Hodgkin lymphomas and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). In contrast to CHL, most other lymphoma types analyzed showed either variable or no expression of GLI3. A minor subset of cases of NLPHL, anaplastic large cell lymphoma, and gray zone lymphoma showed a GLI3 staining pattern indistinguishable from CHL. In conclusion, the tumor cells in CHL show a distinctive GLI3 expression pattern that is not usually seen in other lymphoma types. This finding suggests that GLI3 can serve as a diagnostic marker in helping to distinguish CHL from mimickers. In addition, our findings suggest that HH signaling may contribute to the pathogenesis of CHL.

P025

MULTI-COLOUR IMMUNOFLUORESCENCE IMAGING OF PARAFFIN-EMBEDDED HODGKIN LYMPHOMA LYMPH NODES

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The identification of Hodgkin and Reed-Sternberg (HRS) cells by immunohistochemistry requires staining with several markers, since HRS cells are generally thought to be CD15+CD30+CD45-CD20-. In the clinic, sequential sections of paraffin-embedded Hodgkin Lymphoma (HL) tissue are usually examined using single colour immunohistochemical stains, making it difficult to unequivocally identify HRS cells. Immunofluorescence microscopy is a useful technique in this context since it not only allows the simultaneous staining of several markers, but also allows a semi-quantitive evaluation of marker expression. It is often

used on frozen tissue, but to date has been applied only rarely to formalin-fixed paraffin-embedded (FFPE) tissue, in part due to problems with tissue autofluorescence. We have developed a multi-colour immunofluorescence technique that enables the simultaneous visualisation of up to four markers in FFPE tissue. In this study, we analysed lymph node tissue from the diagnostic biopsies of patients with HL. Our results show that it is feasible to unequivocally identify HRS cells in a single section by simultaneously staining for CD15, CD30, CD20 (or CD45) and the nuclear marker DAPI. In addition, preliminary results suggest that there are differences in expression patterns of these markers between different HRS cells, including variation in the intensity of each marker, and that these markers have variable localisation patterns within HRS cells. In addition to the HRS cell itself, the tumour microenvironment is believed to have a major impact on the clinical course of HL. In particular, several markers expressed within the tumour stroma have been suggested to have prognostic value, including TIA-1 and CD68 as negative prognostic markers and Foxp3 as a positive prognostic marker. We are applying our multi-colour immunofluorescence technique to further characterise the expression of these markers, in particular investigating the cell sub-types expressing these markers and investigating differences of marker expression between different patients in different therapeutic contexts. In summary, we have optimised the processing and staining of FFPE tissue from HL patients for multi-colour immunofluorescence microscopy, enabling unequivocal identification of HRS cells in a single section, as well as investigation of tumour-stroma relationships and their impact on clinical outcome.

P026

JAK2 REARRANGEMENTS, INCLUDING THE NOVEL SEC31A-JAK2 FUSION, ARE RECURRENT IN CLASSICAL HODGKIN LYMPHOMA

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Molecular mechanisms underlying the pathogenesis of classical Hodgkin lymphoma (cHL) are poorly understood. Although no characteristic chromosomal aberration has been identified in cHL, gain and amplification of the 9p24 region harboring JAK2 have frequently been observed. The non-receptor protein tyrosine kinase JAK2 is an important mediator of cytokine signaling and a recurrent target of chromosomal translocations and gain-of-function mutations in several hematological malignancies. The aim of this study was to characterize a novel t(4;9)(q21;p24) found in a case of nodular sclerosis cHL (NScHL), and to determine the *in vitro* and *in vivo* consequences of the fusion resulting from this translocation. FISH with JAK2/9p24 probes demonstrated involvement of this gene in the t(4;9). Extensive interphase FISH analyses of rare Reed-Sternberg cells mapped the 4q21 breakpoint in the SEC31A region. Molecular studies led to the identification of a SEC31A-JAK2 in-frame fusion. The *in vitro* oncogenic potential of SEC31A-JAK2 was demonstrated in the murine hematopoietic Ba/F3 cell line. SEC31A-JAK2 was found to act as a constitutively activated tyrosine kinase that is sensitive to JAK inhibitors. *In vivo*, SEC31A-JAK2 induced a fatal T-lymphoblastic lymphoma (T-LL) or a myeloid hyperplasia in a murine bone marrow transplant model. In addition, we showed that the T-LL was transplantable to secondary recipients. To determine the incidence of JAK2 rearrangements in cHL, we screened 131 cHL cases by FISH and cDNA-based nested PCR, and identified 3 additional cases with JAK2 rearrangements, including one with a SEC31A-JAK2 fusion. In summary, our study showed that JAK2 is recurrently rearranged in cHL. We identified and molecularly characterized the novel t(4;9) resulting in a SEC31A-JAK2 fusion found in two NScHL cases and identified other not yet characterized JAK2 rearrangements in two additional cHL cases. We demonstrated the oncogenic potential of SEC31A-JAK2 both *in vitro* and *in vivo*. Although aberrant expression of various protein tyrosine kinases including JAK2 has been documented in cHL, our results indicate that at least in some cases, this aberration can be driven by a chromosomal translocation. The finding that SEC31A-JAK2 responds to JAK inhibitors indicates that patients with cHL and JAK2 rearrangements may benefit from targeted therapies.

P027

PILOT STUDY TO ASSESS THE CLINICAL SIGNIFICANCE OF TARC AS A BIOMARKER IN HODGKIN LYMPHOMA

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The chemokine TARC (CCL17) is highly expressed by the Hodgkin and Reed-Sternberg cells in classical Hodgkin lymphoma (cHL) and is detectable in serum and plasma samples from cHL patients prior to therapy. We are currently measuring plasma TARC levels in a prospective study aimed at determining whether elevated TARC levels can be used a) in the early diagnosis of cHL, b) as a prognostic marker, c) to monitor early response to treatment and d) as an early indicator of relapse. To date, we have analysed plasma samples from 68 healthy controls and 202 pre-treatment cHL patients; sequential samples from 59 of the cHL patients, including 34 on-treatment samples, were also assayed. On-treatment FDG-PET results were available for 16 patients and 4 were positive. All healthy controls had plasma TARC levels below the assay cut-off of 285 pg/mL; in contrast, 182/202 (90%) of the cHL patients had elevated plasma TARC levels. Many of these patients had extremely high TARC levels. After treatment TARC levels fell quickly and following two cycles of ABVD most patients had TARC levels within the normal range. Of the 12 patients with negative on-treatment FDG-PET scans, 2 had mildly elevated on-treatment TARC levels (369 and 465 pg/mL). One of the four patients with a positive FDG-PET result had grossly elevated plasma TARC (33,000 pg/mL). At some time point following completion of treatment, 13 of the 54 patients had TARC levels above the 285 pg/ml threshold; however, only 4 samples were above 500 pg/ml and one of these was associated with clinical relapse. One patient with refractory disease had normal TARC levels following completion of treatment and at follow-up. These interim results confirm that the vast majority of cHL patients have a high plasma TARC level at the time of diagnosis. High TARC levels following treatment appear to be associated with a poor response to treatment and relapse in some cases; however, some patients with refractory disease appear to have normal TARC levels.

P028

HLA CLASS I AND EBV POSITIVE CLASSICAL HODGKIN LYMPHOMA PATIENTS IN THE CHINESE POPULATION

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In Caucasians, a significantly higher proportion of Epstein Barr virus (EBV)-negative cHL lose HLA class I expression as compared to EBV-positive cHL. In the EBV- cHL patients HLA-A*02 was associated with a reduced whereas A*01 with an increased risk on EBV-positive cHL. The HLA class I expression or the HLA association (in relation to EBV) in Asian cHL patients have not been previously investigated. Formalin-fixed, paraffin embedded tissue blocks were available for 145 cHL patients from 5 hospitals from the Northern part of China. Hematoxylin & Eosin-stained sections were used to reclassify the histological subtypes according to the WHO classification. EBV status was determined by visualization of EBERs in tumor cells using in situ hybridization. Membranous expression of HLA class I was detected by immunohistochemistry using antibodies against HLA class I (HC-10) and beta2-microglobulin. DNA was isolated from FFPE tissues to detect presence of HLA-A*02 by quantitative PCR. Positive EBV status was observed in 40% (58/145) of the Chinese cHL patients. As expected, the percentage of EBV+ cases was much higher in the mixed cellularity subtype (71%) than in the nodular sclerosis subtype (16%) (P<0.001). Expression of HLA class I was observed in 79% of the EBV+ cHL patients and in 30% of the EBV- patients (P<0.001). For detection of the HLA-A*02 allele, 23 cHL cases were excluded due to the poor DNA quality. Among the remaining 122 cases, HLA-A*02 was detected in 71% of the EBV-positive and 64% of the EBV-negative cHL patients (NS). In this Chinese pop-

ulation, the tumor cells of EBV-positive cHL more frequently retain HLA class I expression as compared to the EBV-negative cHL, similar to the Caucasian populations. The inversed correlation between presence of the HLA-A*02 allele and positive EBV status, as observed in Caucasians, is not present in the northern Chinese cHL patients. Differences in ethnic background might explain discrepancies in HLA-A association and EBV-positive cHL in different populations.

P029

INVESTIGATION OF PROTECTIVE AND PREDISPOSING HLA ALLELES IN DUTCH CLASSICAL HODGKIN LYMPHOMA PATIENTS

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Classical Hodgkin lymphoma (cHL) is a complex disease involving both environmental and genetic factors. It has become evident that there are genetic associations between certain HLA alleles and cHL and a strong linkage between certain HLA-A alleles and susceptibility to EBV+ cHL. We performed a case-control study to determine the HLA class I and class II alleles in a Dutch cHL population. *Methods.* HLA genotyping of 295 cHL patients was performed with single nucleotide polymorphisms (SNP) specific probes resulting in two-digit HLA typing for the HLA class I and class II genes. Phenotype frequencies of serologically defined HLA-A, HLA-B and HLA-DR blood donors were retrieved from the database of the blood bank of the UMCG. Frequency differences between these controls and cHL patients (total group and EBV+ and EBV- group separately) were analyzed by Chi-square test. In addition, we analyzed the HLA genotyping data for every probe to assess potential differences between the EBV+ and EBV- cHL group using PLINK. *Results.* Frequencies of HLA-DR4 and HLA-DR7 were significantly decreased and HLA-B5 and HLA-B37 were significantly increased in cHL as compared to the controls. In EBV+ cHL, HLA-A1, HLA-B37 and HLA-DR10 frequencies were significantly increased and HLA-A2 was decreased as compared to the controls. In EBV- cHL, the frequency of HLA-DR5 was significantly increased and that of HLA-DR4 was decreased. The SNP analysis revealed significant differences for 16 HLA-A probes between EBV+ and EBV- cHL. Eight probes that represented a high susceptibility for EBV+ cHL were specific for HLA-A1, whereas the other 8 probes correlated with a low risk for EBV+ cHL were specific for HLA-A2. *Conclusion.* The current study demonstrates that certain HLA alleles might have protective or predisposing effects for cHL in general. In a further analysis taking EBV status into account, we also found both protective and predisposing alleles in the two subgroups. In addition, the present SSOP analysis confirmed the previous findings about the significant differences between HLA-A1 and HLA-A2 in EBV+ and EBV- cHL and further indicates that the HLA-A type is more important for this association than the individual SNPs.

P030

THE EXPRESSION OF PROMYELOCYTIC LEUKAEMIA PROTEINS AND THEIR STRESS EFFECTOR PATHWAYS IN HODGKIN LYMPHOMA

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We are interested in the identification of cellular stress pathways that may be exploited as therapeutic targets in Hodgkin lymphoma. Our focus is a key auditor of cellular stress pathways called the promyelocytic leukaemia nuclear domain. Nuclear domains of PML proteins (PML-NDs) are known to act as signalling nodes in multiple homeostatic processes. Given their role as sensors of injury and arbiters of cell fate, PML-NDs are attractive targets for disruption during tumourigenesis; PML is lost, at the protein level, in cancers of multiple lineage. Interestingly, the role of PML-NDs in driving cell fate decisions has not been established for EBV positive cells, which is surprising given the frequency with which oncogenic DNA viruses disrupt these nuclear domains. We have now analysed PML and PML regulated effector pathways, including the DNA damage response, cell cycle regulation and protein handling pathways, in both EBV positive and negative HL cells. Most anti-PML reagents (even those described as pan-PML) have a limited ability to detect the seven or more isoforms of PML expressed in human cells, some of which co-migrate when analysed by one dimensional PAGE. Following screens of multiple PML antibodies we have now resolved the PML isoforms expressed in HL cell lines by one and two dimensional PAGE. Significant differences in PML expression have been detected using whole cell and fractionated lysates. These differences may contribute to the altered activities of tumour suppressors regulated by PML such as p53, as well as novel tumour suppressor activities that we have recently identified by microarray analyses. PML loss in HL cell lines can occur irrespective of virus infection, indicating that PML depletion confers some advantage to the transformed cell. Given the role of PML in regulating the replicative status of normal and cancer-inducing stem cells (as well as their immediate progenitors), we envisage that these data will be of value in sensitising refractile cancer initiating cells to therapy.

P031

THE HISTONE DEACETYLASE INHIBITOR ENTINOSTAT (SNDX-275) TARGETS HODGKIN LYMPHOMA THROUGH A DUAL MECHANISM OF IMMUNE MODULATION AND APOPTOSIS INDUCTION

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Introduction. Based on recent favorable *in vitro* and *in vivo* activity of several HDACi (histone deacetylase inhibitors) in HL (Hodgkin lymphoma), we investigated the *in vitro* activity of SNDX-275, an oral, class 1 isoform of selective HDACi in HL-derived cell lines. *Materials and methods.* Proliferation and cell death were examined by MTS assay, Annexin-V/PI and FACS analysis. For combination studies, cells were incubated with SNDX-275 (0.1-2 μM) and either gemcitabine (1-20 nM), bortezomib (1-20 nM), obatoclax (0.1-2 μM) or ABT-737 (0.01-0.2 μM) for 72 hours. Gene and protein expression were measured by RT-PCR, Western blot, and immunohistochemistry. A multiplex assay was used to determine 30 cytokines and chemokines. *Results.* SNDX-275 induced cell death in a dose and time dependent manner with an IC50 of 0.4 M. At the molecular level, SNDX-275 increased histone-3 acetylation, up-regulated p21 expression, and activated the intrinsic apoptosis pathway by down-regulating the XIAP (X-linked inhibitor of apoptosis protein), which was associated with activation of Caspase 9 and 3. Similarly to other HDACi, SNDX-275 decreased the expression of anti-apoptotic Bcl-2 and Bcl-xL, while level of Mcl-1 and pro-apoptotic Bax remained the same level. Combination studies demonstrated that SNDX-275 had less synergistic effect when combined with gemcitabine and bortezomib and more when combined with Bcl-2 inhibitors obatoclax and ABT-737. Dysregulated cytokine/chemokine production has been shown previously to contribute to HL pathology, including immune tolerance of the cancer cells. Hence, we measured the effect of SNDX-275 on pathways that may contribute to an anti-tumor immune response. Increased IL12 p40-70, IP10, and RANTES, and decreased IL13, IL4 and TARC levels were found, thus favoring Th1-type cytokines/chemokines. Recent data has demonstrated that a variety of epigenetic-modulating drugs may up-regulate the expression of CTAs (cancer testis antigens), leading to a favorable immune response. SNDX-275 was able to induce CTA expression of SSX2 and NY-ESO only in one cell line whereas MAGE-A4 was induced in both HL cell lines. *Conclusion.* Our studies demonstrate that SNDX-275 has a dual effect on apoptotic and immunomodulatory pathways in HL which can be enhanced by the addition of agents targeting cell survival pathways. Phase 2 studies with SNDX-275 in HL are ongoing, future clinical studies should investigate combinations with SNDX-275.

P032

QUANTITATION OF EBV-DNA IN PERIPHERAL BLOOD IN HODGKIN LYMPHOMA: ASSOCIATIONS WITH OTHER BIOMARKERS AND PATIENT CHARACTERISTICS

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Background. In western countries, the Epstein-Barr virus (EBV) is present in 20-40% of Hodgkin lymphoma (HL) in the malignant Hodgkin/Reed-Sternberg (HRS) cells. Detection and quantitation of cell-free plasma EBV-DNA has been proposed as a biomarker in EBV-associated malignancies, including HL. We analyzed the presence of EBV in HRS cells, peripheral blood compartments, and correlated these data to EBV serology, other circulating biomarkers and clinical characteristics. *Patients and methods.* In a single institution cohort of 93 HL patients, EBV-DNA was quantitated using real-time PCR for the EBNA region in whole blood (WB, n=69), plasma (PL, n=75) and peripheral blood mononuclear cells (MNC, n=74). Cell-free DNA levels were determined using a real-time PCR for the globin gene (n=84), cytokine concentrations were measured in 52 patients. EBV status of HRS cells was studied using in-situ hybridization with EBER. *Results.* EBV-DNA was positive in 32% WB, 21% PL and 20% MNC at HL diagnosis, with concordant WB and PL results in 86% of cases. EBER was present in HRS cells in 32% of cases. EBV-DNA copy number over 1500/mL was predictive for the presence of EBER in HRS cells in 86% and 88% WB and PL, respectively, while EBV copy numbers <1500 had only 55% and 57% PPV for WB and PL. Older patients (>50 years) were frequently EBER-positive (66%), with higher EBV copy numbers (median 12800/mL), while younger patients (<50 years) were less frequent EBER-positive (23%), and copy numbers were lower (median 1200/mL) (P=0.01). EBER-positive HL cases frequently had EBNA-1 antibody titers <100 U/mL when compared to EBER-negative cases (44% vs. 13%, P=0.01), and there was a trend for a negative correlation between EBV copy number and EBNA1 titers (P=0.07). In patients with EBER+ HL the plasma EBV-DNA copy number correlated to the level of circulating cell-free DNA (rho=0.65), IL-10 levels (rho=0.87) and inflammation parameters, including CRP (rho=0.79) and ESR (rho=0.57) (all P<0.02), and were higher in stage IV disease (P=0.02). *Conclusions.* High EBV-copy numbers in whole blood and/or plasma at HL diagnosis are not only associated to EBV-status, but are also indicators of disease activity.

P033

OUTCOME-RELATED PROTEIN EXPRESSION PROFILE IN PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA

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Background. The treatment results in patients with relapsed/refractory classical Hodgkin lymphoma (cHL) are often still unfavorable. Thus, there is a need to identify prognostic markers that can identify cHL patients, who may benefit from an intensified upfront approach as compared to conventional therapy. Studies indicate that outcome in cHL patients may be related to tumor microenvironment and not only to the tumor cells. In order to better characterize tumor microenvironmental features of potential prognostic significance, we investigated protein expression profile in total lymph node extracts of cHL patients. *Aim.* To compare protein expression pattern in tumors of cHL patients with favorable and unfavourable outcomes, respectively following first treatment. *Methods.* Frozen tissue samples from 14 patients with advanced stage cHL were identified from archives of the pathology departments and clinical data were obtained from the database of the Danish Lymphoma Group. Of the 14 identified patients, 7 had chemosensitive disease with favorable outcome following first line therapy and 7 displayed relapsed/refractory disease upon first line treatment. Tissues were subjected to high-resolution two-dimensional gel electrophoresis. Individual protein spots were visualised with silver staining and the expression profile in the favorable and unfavorable groups were compared by computer analysis. Proteins with two fold or more differential expression between the two clinical groups were identified by liquid chromatography tandem mass spectrometry and further studied by immunological methods. *Results.* This study confirms the feasibility of using archival frozen tissues from cHL patients for proteomic analysis using our protocol. The protein expression profiles of the two clinical groups analyzed showed significant and distinct differences. One of the differentially expressed proteins was identified as galectin-1 which was overexpressed in the patient subset with poorer outcome. This differential expression was further verified by western blotting. *Conclusions.* Significant differences between samples from patients experiencing favorable versus unfavorable treatment outcome were found. Overexpression of galectin-1 in unfavorable cHL may provide further insight into the pathophysiology of the disease.

P034

CONSTITUTIVE ACTIVATION OF AKT AND ERK KINASES IS RESPONSIBLE FOR FOXO1 REPRESSION IN CLASSICAL HODGKIN LYMPHOMA

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The FOXO transcription factors control proliferation and apoptosis in different cell types. Their activity is regulated by posttranslational modifications such as phosphorylation by the protein kinase B (PKB), ERK, IKK and others. This phosphorylation controls nuclear export and degradation. We show by immunohistochemistry (IHC) and quantitative PCR (Q-PCR) that FOXO1 is highly expressed in reactive germinal center B cells. High expression of FOXO1 was also found in most of non-Hodgkin lymphomas. In contrast, quantitative RT- PCR (Q-PCR) revealed that FOXO1 expression is down-regulated in classical Hodgkin lymphoma (cHL)-derived cell lines. In 31 of 32 cHL cases, Hodgkin Reed-Sternberg (HRS) cells were FOXO1 negative. Ectopic expression of a constitutively active FOXO1 protein blocked proliferation and induced apoptosis in the cHL cell lines L428 and KM-H2. Interestingly, FOXO3 also inhibited proliferation of both cell lines. Inhibition of proliferation was associated with G0/G1-arrest, down-regulation of CCND2 and the up-regulation of CDKN1A expression. Induction of apoptosis correlated with induction of the pro-apoptotic FOXO target gene PMAIP1/NOXA or BCL2L11/BIM. We found that an inhibitor of AKT/PKB activation, KP372-1, and an inhibitor of MEK1/2, U01236, restored FOXO1 expression in cHL cells. The efficacy of the inhibitors correlated with the activation status of their targets. KP372-1 increased FOXO1 expression selectively in L1236 and in SUP-HD1 cHL cell lines, in which AKT was constitutively active. U0126 increased FOXO1 expression in KM-H2, L428, UHO1, and SUP-HD1 cell lines demonstrating characteristic ERK activation, but not in L1236 cell line, in which ERK phosphorylation was not detected. Our data suggest a critical role of FOXO1 repression in the pathogenesis of cHL.

P035

EPIGENETIC SILENCING OF TUMOR SUPPRESSOR GENE KLF4 IS A COMMON EVENT IN B-CELL LYMPHOMAS

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The Kruppel-like factor 4 (KLF4) is a versatile transcription factor that may act both as an oncogene and a tumor suppressor in a context-dependent manner. In models of T-lymphoma and pre-B-cell lymphoma, KLF4 was demonstrated to act as tumor suppressor. In the present study, we found that the KLF4 promoter is often methylated in B-cell lymphoma cell lines and in primary cases of B-cell lymphomas, namely, follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), Burkitt's lymphoma (BL), as well as in classical Hodgkin lymphoma (cHL). Moreover, hypermethylation of KLF4 promoter was associated with absence of its expression. Promoter CpG island hypermethylation has been established as one of the key mechanisms that silence tumor suppressor genes and promote tumorigenesis. We found conditional over-expression of KLF4 in two BL cell lines moderately retarded their growth, mainly due to cell cycle arrest in the G0/G1 phase. Overexpression of KLF4 in a primary mediastinal B-cell lymphoma cell line MedB1 also induced apoptosis and cell cycle arrest. In the cHL cell lines KM-H2 and L428 KLF4 expression induced massive cell death that could not be inhibited completely with an unspecific caspase inhibitor. Using a quantitative RT-PCR gene expression array we identified KLF4 target genes including the proapoptotic gene BAK1, activation level of which was much higher than

that of other regulators of apoptosis. We further investigated role of BAK1 in KLF4-induced apoptosis in cHL cells. Using a shRNA-mediated knockdown approach we demonstrated that pro-apoptotic protein BAK1 is largely responsible for KLF4-induced cell death. Moreover, KLF4 downregulates musculin (MSC) / activated B-cell factor-1 (ABF-1) in cHL cell lines. Of note, aberrant expression of ABF-1 is proposed to be responsible for the unique loss of B-cell phenotype of cHL. We conclude that epigenetic silencing of KLF4 in B-cell lymphomas not only favors tumor cell survival by loosening cell cycle control and protecting from apoptosis, also contributes to establishment of cHL phenotpye.

P036

CD20 EXPRESSION IN REED-STERNBERG CELLS OF CLASSICAL HODGKIN'S LYMPHOMA: ANALYSIS OF PRESENTING FEATURES AND CLINICAL OUTCOME

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Hodgkin and Reed-Sternberg cells (HRS) cells represent the neoplastic population of classical Hodgkin lymphoma (cHL). Recent immunological and molecular studies have shown that HRS cells originate from mature germinal centre B cells. The prognostic significance of CD20 expression in HRS cells of cHL is still controversial. *Aims and methods.* To further assess the presenting features and the prognostic significance of CD20 expression in cHL, we performed a retrospective single institutional study of 87 cases with a mean clinical follow-up of 12 years. The mean ages were 40.4 years (range, 14-83 years) for the men and 34.3 years (range, 16-77 years) for the women. Sixty-five (74.7%) of the 87 patients (pts) were younger than 45 years of age. The histology were nodular sclerosis in 75, mixed cellularity in 10, lymphocyte rich cHL in 1, and lymphocyte-depleted in 1. Stage III+IV was present in 57 pts (65.5%), bulky disease in 34 pts (39.1%), extranodal disease in 16 (18.4%).57 pts (65.5%) were treated with combined radiochemotherapy, 30 (34.5%) were treated with chemotherapy alone. 24 pts (27.6%) received MOPP/ABVD, 16 (18.4%) received BEACOPP, 47 (54%) received ABVD, chemotherapy regimens. *Results.* HRC expressed CD20 in 27 pts (31% of cases). The negative rate of CD20 was significantly higher in the patients with B-symptoms (54% vs. 32.2%, P=0.046) and with bulky disease (49.4% vs. 22.9%, P=0.035). There was no statistically significant difference in CD20 expression between the groups with other different clinical parameters. No statistical differences in terms of response rate (82% vs. 85%) was found between CD20 positive and negative cHL. The 5-year progression free survival (PFS) rates were 76.2% in CD20-positive patients and 82.2% in CD20-negative patients (P=n.s.; Figure 1). The 5-year overall survival (OS) rates were 91.4% in CD20-positive patients and 92.5% in CD20-negative patients (P=n.s.). *Conclusions.* CD20 is expressed by HRS cells in 31% of patients with cHL. It is higher in the patients without bulky disease and B symptoms. However, according to our results, the expression of CD20 is not an independent prognostic factor for PFS and OS of naive cHL patients.

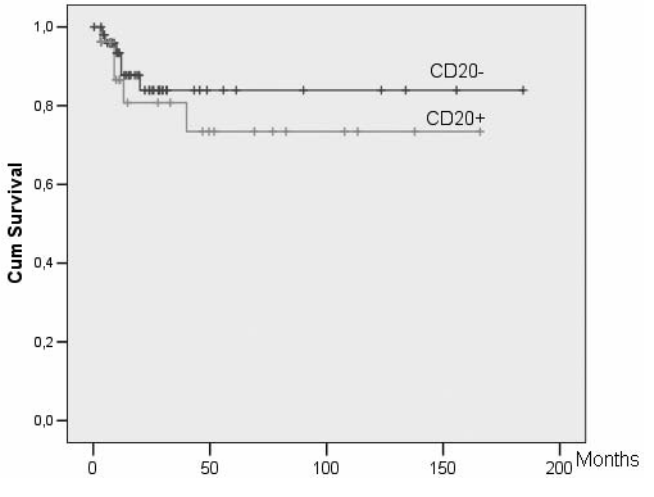

Figure 1. PFS in pts with cHL according to CD20 expression in HRS.

P037

MICRORNA PROFILING OF HRS CELLS IN DIFFERENT HODGKIN LYMPHOMA SUBTYPES

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A hallmark of Hodgkin Lymphoma (HL) is the rare occurrence of malignant Hodgkin/Reed-Sternberg cells within the inflammatory micromilieu of the tumor. The scarcity of these cells has been impeding molecular analyses of HL. In this study, we established a protocol for microRNA (miRNA) profiling of microdissected HRS cells obtained from paraffin-embedded lymph node biopsies. We investigated different HL subtypes, among them CD20$^-$ nodular sclerosis (NS), CD20$^+$ nodular sclerosis (CD20$^+$), mixed cellularity (MC) and lymphocyte predominant (LP) HL. Expression of 360 miRNAs was determined in 22 patients and compared to that of tonsillar germinal center B cells (GCB). Unsupervised clustering analyses revealed significantly different miRNA expression patterns in different HL subtypes. Our data suggest that HL subtypes might be classified by specific miRNA expression patterns. Further analyses concerning differential miRNA expression of HRS and GCB and also between the different HL subtypes are currently conducted.

P038

IMPAIRED NK CELL ACTIVITY IN HODGKIN LYMPHOMA

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Natural Killer (NK)-cells are lymphocytes of the innate immunity, which provide a link to the adaptive immune responses. Hodgkin Lymphoma (HL) patients have impaired NK cell activity in the peripheral blood and the level of NK cell anergy correlates with a bad prognosis. It is known that the local and systemic immune response is negatively affected by the sustained expression and the release of soluble ligands for the cytotoxicity receptors expressed on NK cells. So far, nothing is known about the expression of ligands for NK cell receptors in the sera of Hodgkin Lymphoma (HL) patients. Here, we investigate the serum levels of the ligand HLA-B associated transcript 3 (BAT3) for the cytotoxicity receptor NKp30, to determine if soluble BAT3 might be involved in NK cell inhibition. We screened the sera of 36 healthy donors and 56 early and late stage HL patients using a BAT3 specific sandwich-ELISA and recombinant BAT3 as standard. The BAT3 serum level was significantly elevated in HL patients in comparison to healthy donors (P=0.0002). Interestingly, the early stage patients had a more pronounced increase compared to the advanced stage patients (P=0.024). Cytotoxicity assays with NK cells isolated from HL patients indicate a dramatic reduced killing efficacy against the Hodgkin cell line L540 in comparison to NK cells from healthy donors. In addition, we investigated if an aberrant expression of the activating NK-receptors might contribute to the observed NK cell anergy in HL patients. 4-colour FACS analysis of peripheral blood lymphocytes revealed no significant difference between NK cells analysed from 46 HL patients and 10 healthy controls regarding the expression pattern of NKp30, NKp44, NKp46, NKG2D, CD244 and CD16 or the activation markers CD25, CD69 and CD71. Thus, the enhanced BAT3 serum levels in HL sera do not seem to affect the expression of NKp30 and other receptors pointing towards other mechanisms impeding NK cell activity. The molecular effects responsible for the NK cell inhibition in HL by serum-derived factors will be discussed.

P039

CHARACTERIZATION OF A NEW IAP INHIBITOR IN HODGKIN CELL LINES: DIRECT CYTOTOXICITY AND ACTIVATION OF NATURAL KILLER CELLS

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Even though Hodgkin lymphoma is considered curable in about 80 % of patients, there are severe side effects after therapy including secondary malignancies and organ damage. Therefore, it is important to reduce treatment-related side effects. Currently, molecules that have the potential to repress inhibitor of apoptosis proteins (IAPs) are arousing interest. IAP inhibitors suppress XIAP-mediated Caspase inactivation and lead to NF- B activation, TNF secretion and autocrine TNF -induced cell death. Since NF- B is constitutively activated and the NF- B target XIAP

is strongly expressed in Hodgkin lymphoma, the IAP inhibitor LCL161 was tested for its molecular effects in Hodgkin lymphoma cell lines. LCL161 induced minor apoptosis and only a slight increase in NF- B activity in L428 cells. Interestingly, TNF secretion was reduced after treatment. While an agonistic FAS antibody led to increased apoptosis when combined with LCL161, combinatory effects of IAP inhibitors with Doxorubicin, Bortezomib, TRAIL and TNF have been described in different tumors but were not observed in Hodgkin cell lines. Furthermore, the interactions between NK cells and LCL161-treated cells were investigated. After incubation with LCL161, L428 cells showed increased transcription of NKG2D ligands and NK cells displayed enhanced cytotoxicity against treated cells, which was shown to be NKG2D-dependent. The data suggests that a clinical benefit of LCL161 in Hodgkin lymphoma is rather attributed to the activation of innate immune cells against tumor cells than to a direct cytotoxicity.

P040

DRASTIC TELOMERE SHORTENING IN B AND T LYMPHOCYTES ASSOCIATED TO THE PRESENCE OF 'GHOST' NUCLEUS IN PERIPHERAL BLOOD LYMPHOCYTES OF HODGKIN LYMPHOMA PATIENTS

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Purpose. Hodgkin lymphoma (HL) is a malignancy of the immune system, characterized by scarce Hodgkin and Reed-Sternberg tumor cells which are, in most cases, derived from germinal center B cells. T-lymphocytes are immune system cells that play a major role in regulating immunity in HL patients. Recently, telomere shortening in tumor cells and whole peripheral blood mononuclear cell (PBMNC) has been reported in HL. We investigated telomere analysis of T and B-lymphocytes and of all other circulating nuclei in HL patients. *Patients and methods.* peripheral blood lymphocyte cultures in the presence of PHA (T-lymphocytes) and TPA (B-lymphocytes) from 50 HL patients (mean age 33.5 years, 74% early stage disease and 80% nodular sclerosis) were assessed. Telomere lengths were determined by 3D telomere analysis after quantitative fluorescence in situ hybridization (Q-FISH) technique and TRF assay. *Results.* using Q-FISH, the mean telomere length was 4.4 kb (3-8.6 kb) in B-lymphocytes, 4.7 kb (2.6-7.1 kb) in T-lymphocytes and 7.8 kb (4.7-13.6 kb) in the nucleus (R=0.87, P<10-3). The mean telomere length measured by TRF assay was 8.4 kb (5.5-13kb) (R=0.73, P<10-3 correlation with Q-FISH in nucleus). Thus, we found a significant telomere shortening in T- and B-lymphocytes as compared to the telomere length in the nucleus (whole PBMNC) (reduction of 44%, P<10-3). Telomere analysis in B and T lymphocytes revealed a huge intra cellular heterogeneity in telomere signals and the presence of telomere doublets. We identified the presence of telomere aggregates and 'ghost' nucleus characterized by chromosome pulverisation. These nuclei contents strongly contrast with the corona of surrounding lymphocytes showing amplification of telomere signal and high EBV genome copy number. *Conclusion.* Thus differential alterations of telomere length are observed in both types of lymphoid cells in HL patients. Analysis of chromosomal rearrangements (M-FISH), telomere maintenance (telo-PNA-FISH) and viral infection (EBV and JCV) should permit to identify the potential link between telomere shortening and chromosome instability in those patients.

P041

CTLA4 POLYMORPHISMS INFLUENCE HISTOLOGICAL AND CLINICAL CHARACTERISTICS IN CLASSICAL HODGKIN LYMPHOMA

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The cytotoxic T-lymphocyte antigen-4 gene (CTLA4) encodes an immunoreceptor molecule that inhibits T-cell proliferation. Its polymorphisms appear to differentially influence its inhibitory activity though the efficiency of processing and expression level of the molecule. The CTLA4 CT60GG, +49GG genotypes and -1722G allele were associated with low inhibitory potential (LIP). *Objective.* To investigate if CTLA4 polymorphisms influence the tumor microenvironment composition, clinical characteristics and outcome in cHL. *Methodology.* 132 patients (3-81y, median 15) were included. DNA was extracted from peripheral blood or tumor diagnostic samples. Three CTLA4 polymorphisms (-1722A/G, +49A/G and CT60A/G) were evaluated by allele discrimination TaqMan assays. Lymphocyte population and Ki67 were evaluated for immunohistochemistry in TMA slides. *Results.* The CTLA4 CT60GG genotype (LIP) was associated with a high HRS-cells proliferation index (PI) (Ki67>50%; P=0.039), while it was associated with low number of involved anatomic areas (IAA) (P=0.004), low stages (P=0.038) and low risk-group (P=0.036). Patients bearing the CTLA4-1722G mutant allele (LIP) were also more frequent in the low risk-group (P=0.019). In agreement, the CTLA4 haplotype 49G/CT60G was associated with low PI (P=0.047) and trendily with low stages (P=0.089), while haplotype 49A/CT60A was associated with high risk-group (P=0.02) and a high PI (P=0.053). Haplotypes 49A/CT60A and 49G/CT60G were associated with high and low numbers of T-lymphocytes, respectively (P=0.044 and 0.036) while higher percentages of CD4-T cells were observed in CTLA4+49AA genotype (high-IP) (P=0.06). A better event-free survival (EFS) was associated with the CTLA4+49AA genotype (85.4% to CTLA4 +49AA vs 66.7% in other genotypes; P=0.051), as well as with the presence of EBV in tumor cells (P=0.011). Worst EFS was observed in cases with >4 IAA (P=0.026), extra nodal involvement (P=0.025), leucopenia (P=0.015) and CTLA4 haplotype 49G/CT60G (P=0.02). In the Cox regression, >4IAA (P=0.045) and haplotype 49G/CT60G (P=0.007) maintained the prognostic impact. *Conclusion.* This is the first study to investigate CTLA4 polymorphisms in cHL, and shows a potential effect of CTLA4 variants on cHL clinical presentation, microenvironment, and outcome. CTLA4 may be useful as a prognostic marker and therapeutic target in HL.

P042

THE NOVEL ORGANIC ARSENICAL, DARINAPARSIN (ZIO-101), INDUCES APOPTOSIS THROUGH AKT AND MEK/ERK PATHWAYS IN HODGKIN LYMPHOMA (HL) AND T-CELL LYMPHOMA (TCL) CELL LINES

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Background. The inorganic arsenical, arsenic trioxide (ATO), has a narrow therapeutic index, which has limited its use in most malignancies. Darinaparsin (ZIO-101, S-dimethylarsino-glutathione), synthesized by conjugating dimethylarsenic to glutathione, is a novel organic arsenical that is under investigation as an agent for the treatment of cancer. Early-phase clinical trials with darinaparsin have demonstrated low toxicity and clinical efficacy in relapsed/refractory hematologic malignancies. *Methods.* We treated the HL cell line, L428, and several TCL cell lines (Jurkat, C10MJ, Hut-78, MT2) with increasing concentrations of darinaparsin (0.5-5μM) ± the MEK inhibitor, U0126, or ERK siRNA (Qiagen HiPerFect transfection). Cell survival/apoptosis were measured by MTT and Annexin-V/propidium iodide (flow cytometric). Intracellular drug concentrations were assessed with mass spectrometry, while transcription pathway intermediates were analyzed by Western blotting. *Results.* Darinaparsin inhibited cell growth and induced apoptosis in all cell lines at 1-3μM. At 2μm (48 hours), darinaparsin induced approximately 80% apoptosis in all TCL lines, while 3μM resulted in 65% apoptosis in L428 cells. By comparison, >10μM of ATO (48 hours) was required to induce 40% apoptosis in TCL and 25% apoptosis in L428. At 1-3μM, darinaparsin induced significant increases in caspase 3 and PARP activation in TCL, while minimal caspase or PARP was observed in L428. Notably, in L428 cells at 1-6 hours, mass spectrometry showed that intracellular accumulation of darinaparsin was >10-fold higher as compared with ATO (P<0.05). We also treated L428 cells with U0126 (5μM) or ERK2 siRNA combined with darinaparsin. Pre-incubation with MEK inhibitor or ERK2 knock down followed by treatment with darinaparsin significantly enhanced darinaparsin-induced apoptosis (P<0.05). To further investigate darinaparsin-induced signaling pathways, we analyzed phospho-AKT (p-AKT), and phospho-ERK (p-ERK) in Jurkat and L428. We found down-regulation of p-AKT in Jurkat as well as L428 cells, while total AKT remained unchanged. Additionally, an increase in p–ERK was observed in L428 cells with 2-3μM darinaparsin, while p-ERK was down-regulated in Jurkat cells. *Conclusions.* Altogether, our findings show

that darninaparsin induces significant cell death in HL and TCL cell lines that occurs through AKT and MEK/ERK-based pathways. Continued pre-clinical and clinical trial investigation of darinaparsin in HL and TCL is warranted.

P043

JC HUMAN POLYOMAVIRUS IS ASSOCIATED TO CHROMOSOMAL INSTABILITY IN PERIPHERAL BLOOD LYMPHOCYTES OF HODGKIN LYMPHOMA PATIENTS AND POOR CLINICAL OUTCOME

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Epidemiological, molecular, and immunological features of Hodgkin lymphoma (HL) suggest that viruses could play a role in its progression and clinical outcome, B cells are potential sites for latency and reactivation of the human neurotropic JC polyomavirus (JCV). We investigated JCV and Epstein Barr virus (EBV) status in peripheral blood lymphocytes (PBL) from 74 HL and 91 B-NHL patients. *Patients and methods.* JCV and EBV DNA were assessed by PCR, and FISH technique was used to localize viral infection and to estimate chromosomal instability (rogue cells, chromosomal aberrations) throughout evolution. We screened by haemagglutination inhibition (HI) for serum antibodies to JC virus (JCV) sera of lymphoma patients. The influence of viral infection and of chromosomal instability on freedom-from-progression (FFP) was investigated in HL patients. *Results.* PCR product sequencing of PBL identified JCV in 42 (57%) circulating lymphocytes of HL patients. FISH analysis revealed that the presence of cells with a high JCV genome copy number associated to the presence of rogue cells and higher frequency of chromosomal aberrations increased from 15% before treatment to 52% P<10-5 after. The overall rate of seropositivity for JCV was 86.2% in HL and 63.3% in NHL, as compared to 63% in a population of 98 random blood donors. The co-activation of JCV and EBV was observed in 32%, independent of known prognostic parameters, and associated with a shorter FFP (JCV and EBV co-activation P<0.001, rogue cells P<0.002). *Conclusion.* In HL, JCV activation, chromosomal instability and a higher seroprevalence have been identified in PBL, associated with a poorer prognosis, especially in EBV+. These observations cast a new light on the role of EBV and JCV in the pathogenesis of HL. Monitoring the status of these viruses may contribute to anticipate the clinical course of the disease, and lead to new antiviral and molecular strategies. The genesis of rogue cells is intriguing. The cytogenetic features of HRS cells are reminiscent of those of rogue lymphocytes. The detection of JCV in tumor cells of Hodgkin-involved nodes could help answer these questions.

P044

HLA EXPRESSION AND GENETIC ASSOCIATIONS IN EBV POSITIVE AND EBV NEGATIVE CLASSICAL HODGKIN LYMPHOMA

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Extensive cross-talk between Hodgkin Reed-Sternberg (HRS) cells and the reactive infiltrate is essential in the pathogenesis of classical Hodgkin lymphoma (cHL). The reactive infiltrate provides survival signals for the HRS cells, while the HRS cells produce factors to prevent an effective anti-tumor response. Escape of HRS cells from anti-tumor immune responses involves modulation of antigen presentation. In the past years we further studied genetic associations and functionality of HLA expression in both EBV+ and EBV- cHL. We previously showed that the HLA-A*01 type predisposes to the development of EBV$^+$ cHL, while the HLA-A*02 type is protective. Intuitively, this can be explained by the generally acknowledged lack of HLA-A*01 restricted immune responses to latent EBV peptides. By extensive HLA typing we now show minor effects of other HLA alleles in EBV$^+$ cHL. In addition, we found associations of HLA class II alleles with susceptibility to EBV$^-$ cHL as well. Another strategy to escape immune responses is down regulation of HRS cell surface expression of HLA molecules. Indeed, in EBV$^+$ cHL patients that carry the protective HLA-A*02 allele, down regulation of HLA class I occurs more frequently. In addition, the pattern of HLA class II down regulation is different in Chinese and Dutch populations, suggesting that the genetic background influences the magnitude of selection pressure on down regulation of HLA. In the Dutch population, lack of HRS cell surface HLA class II can be seen in 40% of cHL patients, is an independent adverse prognostic factor and is associated with extranodal disease and EBV$^-$ cHL. Of note, cell surface expression of HLA class II does not necessarily mean that antigenic peptides are presented. We have found that lack of HLA-DM expression by HRS cells results in cell surface presentation of the non-immunogenic class II associated invariant chain CLIP peptide in approximately half of HLA class II positive cHL patients. In conclusion, genetic HLA associations with EBV+ and EBV$^-$ cHL confirm that antigen presentation is intricately involved in the pathogenesis of cHL. Functional studies are needed to identify which antigenic peptides are involved.

P045

UGT1A1 GENE PHARMACOGENETICS IN THE TREATMENT OF HODGKIN'S LYMPHOMA

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Introduction. The aim of pharmacogenetics is to study the association between patient's genetics and treatment response and toxicity. This association has already been demonstrated in some neoplasms. Significant differences in the evolution of a group of 313 patients with Hodgkin lymphoma (HL) and treated with ABVD depending on UGT1A1 genotype have recently been described. Those patients with homozygous genotype with 6 repetitions TA had worse prognosis than the others. *Objective.* To confirm if UGT1A1 genotype modifies the survival and toxicity in a group of patients with HL treated with first line ABVD. *Materials and methods.* This retrospective analysis includes those patients diagnosed of HL in the different participant centres from January 2006 to December 2009 and treated with first-line ABVD. All the patients were genotyped for UGT1A1 gene and their medical history and clinical evolution was reviewed. *Results.* One hundred and fifty two patients have been included, 84 males and 68 females. Mean age at diagnosis was 39 years (15-87). Histological subtype was nodular sclerosis (n=97), unspecified classical subtype (n=24), mixed-cellularity subtype (n=15), lymphocyte-rich (n=6), lymphocyte-nodular predominance (n=5) and unclassifiable (n=5). Eighty-nine patients were diagnosed in stages I-II and 63 in an advanced stages; 60 patients presented B symptoms at diagnosis. Mean number of ABVD cycles administered was 6 (2-8). Sixty-six patients received radiation therapy combined with chemotherapy. One hundred and thirteen patients have been genotyped for UGT1A1 gene (51:TA6/TA6, 47:TA6/TA7 and 15: TA7/TA7). The response rate (complete remission / partial remission) was not modified by the genotype. With a median follow up of 22 months, UGT1A1 genotype did not significantly influence either overall survival, progression free survival, time to progression or disease free survival. In addition, UGT1A1 genotype did not have any significant impact on the haematological toxicity of ABVD (measured by the use of G-CSF and delays in chemotherapy administration). *Conclusion.* In our group of patients with HL treated with ABVD as first-line therapy, UGT1A1 genotype did not seem to be significantly associated to response rate, survival or toxicity.

Early Stages

C046

EARLY FDG-PET SCAN CONFIRMS ITS PROGNOSTIC IMPACT ALSO IN LOCALIZED STAGE, ABVD TREATED HODGKIN LYMPHOMA PATIENTS

Rigacci L, Zinzani PL, Puccini B, Broccoli A, Gallamini A, Merli F, Antognoli G, Stefoni V, Stelitano C, Balzarotti M, Pregno P, Fraulini C, Salvi F, Emili R, Tavera S, Capodanno I, Vitolo U, Pellegrini C, Liberati AM, Bosi A

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A small proportion of patients with localized stage Hodgkin's disease do not respond to therapy and progressed. We explored the predictive value on therapy outcome of an early evaluation of treatment response by 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) scan performed after two corses of ABVD in pts with localized Hodgkin's disease. From 2002 to 2008, 246 new localized stage Hodgkin's lymphoma pts were consecutively admitted to twelve Italian hematological centers. Pts with stage I-IIA, independent of presence of bulky disease, were considered for the study. FDG-PET was mandatory at baseline, after two cycles and at the end of therapy. Mediastinal blood pool activity is recommended as the reference background activity to define PET positivity. No treatment variation based only on PET-2 results was allowed. The median age was 33 years (14-78), 133 pts were female, 225 pts were stage II, bulky was reported in 76 pts. 231 pts were treated with combined modality. The FDG-PET performed after two cycles (PET2) was positive in 34 pts (14%): 18 (53%) progressed or relapsed and 14 obtained CR. By contrast 202/212 (95%) pts with a negative PET2 remained in CR. Thus the positive predictive value (PPV) of a PET2 was 59% and the negative predictive value (NPV) was 95%. If we consider non bulky disease pts PPV increase to 71% and NPV to 98%, the sensitivity and specificity were 80% and 97%, respectively. In univariate analysis negative FDG-PET performed after two cycles (P .0000), absence of bulky disease at diagnosis (.01) were statistically correlated with a better progression free survival. In multivariate analysis only PET2 was independently predictive of relapse/progression probability (P .000). With a median follow-up of 35 months (range 4-87) 238 ùpts are alive. The 2-yr FFS probability for PET2 negative and for PET2 positive patients were 97% and 30% respectively (P: .000). This multicentric study confirms that PET2 was able to predict treatment outcome also in early stage Hodgkin disease. Due to the large number of false positive PET2 in localized lymphoma with bulky disease we suggest new PET evaluation methods in this subset of pts.

C047

INVOLVED NODE RADIOTHERAPY SIGNIFICANTLY REDUCES LUNG, BREAST AND THYROID DOSE IN PATIENTS WITH LIMITED STAGE HODGKIN LYMPHOMA

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Purpose. Chemotherapy plus consolidation radiotherapy (RT) is the standard of care to treat limited stage Hodgkin lymphoma (HL), achieving 90% overall survival at 10 years. However, long term survivors are at risk of RT-induced late toxicities including second malignancy. The evolution from involved field (IFRT) to involved node radiotherapy (INRT) aims to decrease RT morbidity without compromising cure rates. To date, there are no clinical data documenting late toxicity advantages from INRT. *Methods.* Ten previously treated female patients with stage IA or IIA, non bulky, supradiaphragmatic HL were randomly selected. Eligibility required: staging CT and PET, treatment with ABVD chemotherapy plus RT, CT-simulation. Per patient, IFRT and INRT plans were created, using parallel-opposed, 6MV photon beams. Clinical target volume (CTV) covered the pre-chemotherapy involved nodal volume, within post-chemotherapy anatomical boundaries. For INRT, the margins from CTV to planning target volume for mediastinal and hilar nodes were 2 cm cranio-caudally and 1.5 cm radially; margins were 1cm for all other sites. For IFRT planning, the German Hodgkin Study Group protocol was used. Organs at risk (OAR) were contoured: lungs, breasts, thyroid, heart, and coronary artery origins. For each OAR, the calculated dose parameters for IFRT and INRT were compared. The prescription dose was 30.6Gy in 1.8Gy/fraction. *Results.* Patient characteristics: median age, 32 years; stage IA, 3; stage IIA, 7. Reducing the field size from IFRT to INRT resulted in relative reductions in mean doses to OAR: 30% lungs, 34% breasts, 56% thyroid, 35% heart, <1% coronary artery origins. On Wilcoxon non-parametric testing, INRT significantly reduced mean dose, V1, V20 and D50 for lungs (P<0.01 for all parameters), breasts (P<0.01 for all parameters), and thyroid (P<0.03 for all parameters). INRT significantly reduced mean cardiac dose (P<0.01) and D50 (P=0.01), but not V30 (P=0.55). For coronary arteries, there were no significant reductions in mean dose (P=0.77) or D50 (P=0.80). *Conclusion.* In this study population, reduction from IFRT to INRT significantly improved dose parameters for lungs, breasts and thyroid; we extrapolate that the risk of second malignancy is likely to be reduced in these OAR. Coronary artery dose was unaffected by reduced RT field size.

P048

CONTRIBUTION OF PET /CT IN THE DESIGN OF THE INVOLVED NODE RADIOTHERAPY (INRT) CONCEPT FOR PATIENTS WITH LOCALIZED HODGKIN LYMPHOMA: PRELIMINARY RESULTS ON 117 PATIENTS ENTERED IN THE H10 TRIAL

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Background. The INRT concept requires an extremely precise determination of the number and volume of initially involved nodes. In the study, we tried to assess the additional value of a PET/CT performed before treatment. *Patients and methods.* Early-stage lymphoma patients entered in the EORTC-GELA-IIL. Data imaging comprising PET/CT prior to treatment and CT simulation prior to radiotherapy were retrieved using the DICOM/DICOM-RT imaging network connecting all French cancer centers participating in the H10 trial. A lymph node was considered to be involved if it fulfilled 3 requirements: FDG uptake was greater than the background, was clearly identifiable on CT, and either decreased or disappeared after chemotherapy. Involved lymph nodes were delineated on CT first before adding the information provided by PET. Differences between the number of involved lymph nodes and areas were compared before and after PET/CT assessment. *Results.* From March 2007 to February 2010, 117 patients from 18 French Cancer Centers and hospitals were included in the study. PET/CT identified at least one additional FDG-avid lymph node in 82/117 patients (70%; CI 95%: 61-78%). Additional lymph nodes were observed significantly (P=0.008) more frequently when PET/CT was performed without IV contrast (in 79% of the patients versus 56%). At least one additional lymph node area was detected by PETin 49/117 patients (42%; CI 95%: 33-51%). There was a 15% (CI 95%:9-22%) increase in the gross target volume (GTV) due to the additional information provided by PET (a 20% increase in 10% of the patients). On the other hand, after chemotherapy, there was a 10% (CI 95%:5-18%) increase in the clinical target volume (CTV) in the 96 assessable patients (a 20% increase in 10% of the patients). *Conclusions.* PET/CT with IV contrast is a fundamental imaging procedure forimplementing the INRT concept.

P049

20-YEAR EXPERIENCE IN RADIO- AND COMBINED TREATMENT OF PATIENTS WITH HODGKIN S LYMPHOMA (HL) STAGE II: THE ROLE OF THE IRRADIATION VOLUME AND FRACTIONATION

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Purpose. To study the efficiency of radio- and combined treatment of patients (pts) with HL stage II with different irradiation volume and fractionation. *Material and methods.* 178 pts with HL stage II 15-68 years old (mean age 28.5 years, male-53, female-126) completed only radio- (39) or chemoradioherapy (140) in 1986-2006. Radiotherapy alone in volume of subtotal nodal radiation (STNI) received 23 pts in multifractionation regimen (MR) – 1.2-1.35 Gy twice a day and 16 pts – in usual fractionation regimen (UR). Combined treatment was begun

with COPP/CVPP or ABVD and completed with STNI - 30-36 Gy - in UR (31 pts) or MR (65 pts), or with radiation of primary involved zones (IF) (30-36 Gy) in MR (44 pts). Average time of follow-up in group of pts who received radiotherapy in MR and UR was similar: 91.7 5.2 months and 100 7.6 months, respectively. *Results.* 178 pts (99.4%) entered the state of remission. Recurrences induced in 22 (12.4%) pts and almost twice higher it was observed as a whole in group with UR (9 out of 47 pts, 19.2%, P=0.05) than that in MR (13 out of 131 pts, 9.9%, P=0.05).Quantity of early recurrences was twice lower in MR-group, than that in UR-group (2 pts out of 131, 1.5% and 4 out of 47 pts –8.5% respectively, P<0.03). Recurrences developed significantly later in MR-group, than those in UR: 55.5 7.7 months (21-125 months) and 33.5 7.5 months (7-85 months), respectively, P<0.05. Overall and recurrence-free 10-year survival of combined treatment group with IF radiation in MR was 97.3% and 100%, in groups of combined treatment with STNI in MR it was 84.6% and 80.9% and combined treatment with STNI in UR - 78.1% and 73.2% respectively. *Conclusions.* The more effective schedule of therapy of HL pts stage II is ABVD with IF radiotherapy in MR 30-36 Gy.

P050

A RESPONSE-BASED ABVD REGIMEN WITH OR WITHOUT RADIOTHERAPY FOR PEDIATRIC LOW AND INTERMEDIATE RISK HODGKIN LYMPHOMA IN CENTRAL AMERICA AND DOMINICAN REPUBLIC A REPORT FROM AHOPCA

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Purpose. We hypothesized that in low-risk (LR - stage IA, IIA without bulky disease, less than 4 nodal regions) and intermediate-risk (IR - stage IA or IIA bulky disease, IB, IIA with more than 4 nodal regions, or stage IIIA) patients a response-based therapy with low-dose involved-field radiotherapy (IFRT) would maintain excellent survival and decrease acute and long term toxicity. *Methods.* LR patients received 4 cycles ABVD (adriamicine 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2 on days 1 and 14 of every 28-day cycle). IFRT (2500 cGys) was prescribed only to patients that did not achieve a complete response (CR) after the second cycle of ABVD. IR patients received 6 cycles of ABVD and IFRT (2000 or 2500 cGys) at the end of all chemotherapy, according to rapid early response (RER) status after 4 cycles of ABVD. Toxicities were assessed according to CTCAE 3.0 criteria. *Results.* From 1/2004 to 12/2009, 169 evaluable (107 IR and 62 LR) patients with a median age of 7.8 years were treated with this regimen. Nine (70%) of the LR patients were RER did not require IFRT, and 60% of IR patients were RER and only required 2000 cGy, 11 patients were still awaiting radiation. With a median follow-up time of 2 years we have not observed any relapses or deaths (100% EFS and OS). Six patients abandoned therapy prior to completion (all IR) and 3 patients (1 LR and 2 IR) were lost to follow up after therapy. There were no grade 4/5 toxicities; grade 3 myelosuppression was the most significant yet rare side effect, followed by infections. *Conclusions.* This regimen was well tolerated and produced excellent results. Abandonment in the higher risk group is still the greatest problem and earlier and more aggressive interventions are needed to target this group.

P051

COMBINED MODALITY THERAPY FOR EARLY STAGE HODGKIN DISEASE. ONE CENTER EXPERIENCE

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Introduction. Evaluation of treatment of early stage, favorable and unfavorable Hodgkin disease (HD), according to German Hodgkin Study Group (GHSG), with ABVD (Adriamycin, Bleomycin, Vinblastine, Deticene) and radiotherapy (RT). *Methods.* The favorable group was consisted of 55 patients, with median age 33 years (range 15-71) and median follow-up 34 months (range 5-146). The standard chemotherapy regiment for all patients was 2-4 cycles of ABVD. Fifty-two patients received involved field (IF) radiation (median dose 30 Gy, range 15-39), and three extended field (EF) (median dose 33 Gy, range 30-36). The unfavorable group was consisted of 65 patients, with median age 28 years (range 15-73) and median follow-up 64 months (range 4-172). Twenty-eight patients received 4 cycles and 37 received 6 cycles of ABVD. Fifty-three patients were treated with IF radiation (median dose 30 Gy, range 16-36) and 12 patients with EF (median dose 36 Gy, range 30-45). *Results.* In the favorable group 51 patients (93%) are still in complete remission (CR). Four patients relapsed, from whom all were rescued with salvage chemotherapy and two of them with autologous stem cell transplantation (ASCT). Disease free survival (DFS) was 91% at 5 years, and overall survival (OS) was 100%. In the unfavorable group 55 patients (85%) are still in CR. Ten patients relapsed, all were rescued with salvage chemotherapy, 5 underwent ASCT and one patient died from disease. Total 5-year DFS and OS were 84% and 98%, respectively. Interestingly, patients who received 4 cycles ABVD had 5-year DFS and OS 88% and 100%, respectively, versus 80% and 97% in patients who received 6 cycles ABVD. No patients from both groups developed secondary solid tumor or hematological malignancy. *Discussion.* In early stage HD, the combination of ABVD and irradiation is a highly effective and safe treatment. In early unfavorable group, four cycles of ABVD seems to be an efficient approach with less toxicity. Patients after relapse can be effectively rescued with salvage therapy and ASCT.

P052

RESPIRATORY GATED RADIOTHERAPY DELIVERY (RGRT) IN PATIENTS WITH EARLY STAGE HODGKIN LYMPHOMA (HL): MAGNITUDE OF THE ADVANTAGE

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Purpose. To evaluate dosimetric advantages and Normal Tissue Complication Probabilities (NTCP) for heart and lungs of Respiratory Gated Radiotherapy Delivery (RGRT) in Hodgkin Lymphoma (HL) patients. *Material and methods.* A retrospective planning study was performed on data of ten early-stage HL patients (F/M:6/4; median age: 32; range: 20-43) with predominant mediastinal involvement. CT scans were taken in supine position with the arms alongside the body. Clinical target volumes (CTV), defined as the post-chemotherapy volumes of the pre-chemotherapy involved nodes (INRT), were delineated on the a contrast-enhanced non-gated CT-scan (CT-baseline) and on the maximal inspiratory (CT-insp) and end-expiratory (CT-exp) 4D-CT scans. To generate planning target volumes (PTV) a 0.7 cm margin was added. Lungs and heart were defined as organs at risk (OAR), as well as the coronary arteries, aortic and pulmonic valves, heart ventricles and atria. 3D-conformal plans were created for each patient on all CT sets using Varian/Eclipse® treatment planning software to a prescribed dose of 30Gy/2Gy. For radiobiological plan comparison the risk of developing grade 2 pneumonitis, cardiac mortality and cardiac perfusion defects were calculated with NTCPs. p-values were calculated with the paired t-test (CT-baseline vs CT-insp and CT-exp) and considered statistically significant if <0.05. *Results.* Similar PTV coverage was obtained in all plans. Mean values of OAR dose-volume parameters, NTCP's and corresponding p-values are shown in the Table 1. *Conclusion.* Due to the low baseline risk of pneu-

monitis, cardiac mortality and left ventricular perfusion defects after INRT in early-stage HL, the use of RGRT could not significantly improve outcomes. Moreover, the proximity of the involved nodes to the OAR hampers the potential benefit of RGRT. Detailed analysis, however, revealed large anatomic differences, suggesting that RGRT or Intensity Modulated Radiotherapy may improve outcome in selected patients.

Table 1.

	Baseline plan	*Maximal-inspiratory plan*		*End-expiratory plan*	
V_{95}PTV (%)	95.07	94.89	p=0.34	94.98	p=0.87
Mean Lungs Dose (Gy)	6.63	6.15	p=0.009	6.67	p=0.61
V_{lung}20 (%)	16.89	15.53	p=0.01	16.27	p=0.83
Mean Heart Dose (Gy)	3.80	3.34	p=0.25	4.38	p=0.005
V_{heart}30 (%)	0.56	0.34	p=0.32	0.54	p=0.67
Mean-NTCP-Lungs (%)	1.1	0.9	p=0.08	1.1	p=0.31
Mean-NTCP-Heart (%)	0.18	0.12	p=0.31	0.21	p=0.11
Mean-NTCP-Left Ventricle (%)	14.5	12.9	p=0.36	16.5	p=0.13

P053

ABVD CHEMOTHERAPY IS CRITICAL IN THE TREATMENT OF LIMITED STAGE NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA (NLPHL)

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Background. The appropriate therapy for limited stage NLPHL is unclear. With favorable outcomes reported across multiple studies, attempts have been made to reduce acute toxicity. As a result, in contrast to classical Hodgkin lymphoma, chemotherapy is often omitted; however, whether this omission affects outcome is unknown. We evaluated the outcome of patients with limited stage NLPHL treated with ABVD-like chemotherapy in comparison to radiotherapy alone. *Patients and methods.* We used the BC Cancer Agency Lymphoid Cancer Database to identify all patients with limited stage NLPHL (stage IA, 1B, 2A, non-bulky (<10 cm)). Following pathologic review, 72 patients were identified with NLPHL who were treated based on era-specific guidelines as follows: Before 1993 extended field radiotherapy (RT); 1993-1995 ABVD-like chemotherapy with extended field (1993-1995) or involved field or involved nodal RT (1995-2008) except for 11 patients who received ABVD alone. *Results.* The majority of patients were male, with a median age of 36 y. 26 were treated with RT alone and 2 underwent surgical resection. 44 patients were treated with ABVD-like chemotherapy ± RT. There was no difference in baseline characteristics between the treatment groups. With a median follow-up of 6.25 years (range 2-29 years), the 10 year progression-free (PFS) and overall survival (OS) of the whole cohort were 86% and 93%, respectively. The PFS of patients treated with ABVD-like chemotherapy (± radiotherapy) was far superior to that of patients treated with RT alone (15 y PFS 92% vs 59%, P=0.015) and there have been no lymphoma relapses or deaths to date in the chemotherapy group. The OS was similar (15 y OS 93% vs 83%, P=.180) and most deaths were related to secondary malignancies. In multivariate analysis, treatment with ABVD was the only factor impacting PFS (HR 0.111 (CI 0.013, 0.910, P=0.041). *Conclusion.* The inclusion of ABVD chemotherapy in the primary treatment of limited stage NLPHL results in more durable remissions than RT alone thus minimizing exposure to the potential long term effects of a treatment for relapse in this otherwise young, at risk patient population.

P054

FDG PET/CT SCAN GUIDED TREATMENT OF LIMITED STAGE HODGKIN LYMPHOMA SPARES > 80% OF PATIENTS FROM RADIOTHERAPY WHILE RETAINING EXCELLENT DISEASE CONTROL

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Background. Currently almost all patients with limited stage Hodgkin lymphoma (HL) are cured. Optimal treatment must preserve a very high cure rate while minimizing long term toxicity, particularly gonadal, cardiac and neoplastic. Treatment policy in BC (population 4.5 M) is uniform for the entire province enabling examination of the impact of treatment policies on an entire population. *Methods.* All adult (age >15 y) patients with limited stage (IA, IB or IIA with bulk <10 cm, ±E lesions) HL have been treated with FDG-PET/CT (PET) scan guided therapy (ABVD ×2, then PET: PET negative->ABVD ×2 (total ABVD cycles=4); PET positive or indeterminate->involved field or involved nodal radiation (RT)) since 2004 regardless of co-morbidity. We examined outcome through 2010 for all 117 patients. *Results.* Patient characteristics: age range 17-80 y, median 31, >45 29%, >60 13%; nodular sclerosis 60%, nodular lymphocyte predominant 14%, mixed cellularity 12%, classical otherwise unclassifiable 11%, lymphocyte rich 3%; males 57%; performance status 0-1 97%, 2 3%; stage IA 24%, IB 3%, IIA 70%, IIAE 3%; mass size range 1-9 cm, median 4 cm, >5 cm 40%. Outcome: follow-up range 3-66 months, median 33 months, longest interval to relapse=18 months, follow-up >18 months 82%. Of the 117 patients, 96 (82%) had a negative PET after ABVD ×2 and completed treatment with ABVD ×2 (1 patient received RT instead of ABVD ×2); 4 have relapsed (1 within potential initial RT field, 3 outside); 21 had a positive (n=16) or indeterminate (n=5) PET and received RT; 2 have relapsed, both within the RT field. Of the 6 relapsed patients, 5 have been treated with high dose chemotherapy and autologous stem cell transplant, 1 elderly patient with CVPP+IFRT. No patient has died due to HL or treatment; one 72 y old man with known coronary artery disease died suddenly 7 months after ABVD ×2 + IFRT. Overall 5 y PFS is 96% and 5 y OS is 98%. *Conclusion.* PET guided treatment of limited stage HL achieves excellent disease control while sparing >80% of patients from radiation exposure.

P055

INVOLVED-NODE RADIOTHERAPY (INRT) AND MODERN RADIATION TREATMENT TECHNIQUES IN PATIENTS WITH HODGKIN LYMPHOMA

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Purpose. To assess the clinical outcome of the involved-node radiotherapy concept with the use of modern radiation treatments (intensity modulated radiotherapy (IMRT) or deep-inspiration breath-hold radiotherapy (DIBH)) in patients with localized supra-diaphragmatic Hodgkin lymphoma. *Patients And Methods.* All patients were early stage Hodgkin lymphoma and treated with chemotherapy prior to irradiation. Radiation treatments were delivered using the involved-node radiotherapy (INRT) concept according to the EORTC guidelines. IMRT was performed free-breathing. For the adapted breath-hold technique, a spirometer dedicated to DIBH radiotherapy was used. Three-dimensional (3D) conformal radiotherapy was performed in those patients. *Results.* Fifty patients with Hodgkin lymphoma (48 patients with primary Hodgkin lymphoma, 1 patient with recurrent and 1 with refractory disease) entered the study from January 2003 to August 2008. Thirty-two were treated with IMRT and 18 with DIBH. The median age was 28 years (range 17 to 62). Thirty-four (68%) patients had stage I-IIA and 16 (32%) had stage I-IIB disease. All but 3 patients received 3-6 ABVD. The median radiation dose to patients treated with IMRT and DIBH was respectively 40 grays (Gy) (range: 21.6-40) and 30.6 Gy (range: 19.8-40). Protection of various organs at risk was satisfactory. The median follow-up was 53.4 months (range 19.1-93). The 4-year progression-free and overall survival rates for the whole population were 92% and 98% respectively. Recurrences occurred in 4 patients: 2 were in-field relapses and 2 were visceral recurrences at a distance from the radiation field. Grade 3 acute lung toxicity (transient pneumonitis) occurred in one case. *Conclusions.* Our results suggest that patients with mediastinal Hodgkin lymphoma can be safely and efficiently treated using the INRT concept and modern radiation treatment techniques such as IMRT and DIBH.

P056

IMRT WITH CONCOMITANT THE DEEP-INSPIRATION BREATH-HOLD TECHNIQUE IN PATIENTS WITH MEDIASTINAL HODGKIN LYMPHOMA: BENEFITS AND DRAWBACKS

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Purpose. First to assess the possible additional benefits of using intensity-modulated radiotherapy (IMRT) with the deep-inspiration breath-hold (DIBH) technique in terms of the protection of organs at risk in patients with mediastinal Hodgkin disease; secondly, to evaluate the feasibility in clinical practice of the DIBH modality combined with IMRT. *Materials And Methods.* Patients with early-stage Hodgkin lymphoma and mediastinal tumor masses were studied. Two simulation CT scans were acquired: one on a free-breathing (FB) patient, the other one using the DIBH technique. The clinical target volume (CTV), planning target volume (PTV) and organs at risk were determined on both CT scans according to the EORTC guidelines. Thirty grays (Gy) in 15 fractions were prescribed with IMRT. The dosimetric parameters retrieved for the statistical analysis were: the PTV undercoverage (PTVuc), the mean dose to the heart (MDh) and to the origin of the coronary arteries (MDcoro), the mean lung dose (MDlung) and the total lung volume receiving a total dose exceeding 20 Gy (V20lung). *Results.* There were no significant differences in PTV coverage between the 2 techniques (FB versus DIBH). MDcoro, MDh, MDlung and V20lung were significantly reduced using the breath-hold technique compared with the free-breathing modality (P<0.001). The mean dose delivered to all organs at risk was reduced by approximately 15 to 20%. The dose reduction to organs at risk was greater for mediastinal masses located in the upper mediastinum. IMRT with DIBH was partially implemented in one patient. This combination will be extended to other patients in the near future. *Conclusions.* Radiation exposure of organs at risk in patients with mediastinal Hodgkin lymphoma masses was greatly reduced using the DIBH technique with IMRT. The greatest benefit was obtained for tumours located in the upper mediastinum. The possibility of a wider use in clinical practice is currently being investigated.

P057

BASELINE SERUM C-REACTIVE PROTEIN LEVELS (CRP) IN PATIENTS WITH HODGKIN'S LYMPHOMA (HL) AND ALTERATIONS DURING ABVD CHEMOTHERAPY: CORRELATIONS WITH CLINICAL AND LABORATORY FEATURES AND PROGNOSTIC SIGNIFICANCE

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Background. CRP levels are frequently elevated in HL patients at diagnosis, but powered studies evaluating its association with the outcome are lacking. A negative interim PET is a very strong prognostic factor. CRP alterations might parallel disease activity during chemotherapy, potentially correlated with prognosis. *Aim.* To evaluate baseline CRP and its alterations during ABVD and correlate them with clinicopathological features and outcome. *Patients and methods.* Baseline CRP levels were recorded in 283 patients with HL. Serial CRP measurements prior to ABVD and prior to cycles 1b,2a,3a and 4a were performed in 85 patients. CRP levels at that time-points were analyzed in relation to post-chemotherapy PET and Failure Free Survival (FFS). *Results.* For the 283 patients, the median CRP was 18.6 mg/L; 71% had elevated CRP (>5 mg/L). The 5-year FFS for patients with CRP levels ≤5, 5.01-18.60, 18.61-69.00 and >69.00 mg/L (roughly the CRP quartiles) was 78%, 70%, 62% and 67%. Although the difference was significant for patients with normal versus elevated CRP levels (P=0.03), it was not retained in multivariate analysis (0.10<P<0.20). For the 85 patients with serial CRP determinations, the median baseline CRP was 23.0 mg/L; 72% had elevated CRP. The median CRP levels prior to cycles 1b,2a,3a and 4a were always 3.16 mg/L. The proportion of patients with normal CRP levels increased from 28% at baseline to 72%,69%,78% and 75% prior to cycles 1b,2a,3a and 4a. Post-ABVD PET was positive in 16/74 patients (22%). At a median follow-up of 19 months only 7 patients have progressed for a 2-year FFS of 88%. There was no correlation between interim CRP normalization at any time and post-ABVD PET or FFS. Similar results were obtained when only patients with initially elevated CRP were analyzed. *Conclusions.* CRP levels are elevated in ~70% of HL patients at diagnosis but did not correlate with FFS independently from other established prognostic factors. However, an adverse effect on survival cannot be excluded in the absence of even larger datasets. CRP levels are subjected to very rapid alterations during ABVD chemotherapy. Our preliminary results did not reveal differences in short-term FFS, large enough to be statistically significant.

P058

END OF TREATMENT BUT NOT INTERIM PET SCAN PREDICTS OUTCOME IN NON-BULKY LIMITED STAGE HODGKIN LYMPHOMA

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Introduction. Positron emission tomography (PET) scanning has emerged as an important tool in staging and prognostication of classical Hodgkin lymphoma (cHL). In particular, PET scans early in the course of therapy appear powerfully predictive of outcome, but studies to date have predominantly included patients with advanced stage disease. The prognostic value of interim PET scans in limited stage patients with nonbulky disease has not been established. *Methods.* We queried our comprehensive clinicopathologic database for patients with nonbulky limited stage cHL treated at our institutions between 2000 and 2008. Bulk was defined as a mass ≥10 cm or ≥1/3 of the intrathoracic diameter. Ninety-six patients met criteria and were included in the analysis. All PET scans were centrally reviewed. *Results.* The median age was 34 (range 18-77 years). Seventeen (18%) patients were ≥50 years old, 22 (23%) presented with "B" symptoms, and 8 (8%) had involvement of >3 nodal sites. Eighty-eight percent of patients had stage II disease. Most patients had interim PET performed after either cycle 2 (43%) or cycle 3 (47%). Forty one (43%) patients received 6 cycles of ABVD alone and 54 (56%) received 4-6 cycles of ABVD followed by involved field radiation (30-36Gy). Seventy-nine (82%) patients had a negative interim PET scan, while seventeen (18%) were positive. At a median follow up of 46 months (range 6-107), PFS and OS for the entire cohort are 88% and 97%. Interim PET result had no significant impact on 4-year PFS: 91% vs. 87% (P=0.57). End PET was predictive of outcome with 4-year PFS of 94% in end PET-negative patients vs. 54% in end PET-positive patients (P<0.0001). Four-year OS was likewise superior in end PET-negative patients 100% vs. 84% (P<0.0001). Nine of 17 interim PET-positive patients converted to end PET-negative with a four-year PFS and OS of 89% and 100%, respectively. *Discussion.* The majority of patients in our series with positive interim PET scans were cured of their disease without intensification of chemotherapy. These data do not support treatment intensification based on early PET result in low risk limited-stage patients outside of the context of a clinical trial.

P059

RESULTS OF THE 3RD PLANNED INTERIM ANALYSIS OF THE UK NCRI RAPID TRIAL (INVOLVED FIELD RADIOTHERAPY VERSUS NO FURTHER TREATMENT) IN PATIENTS WITH CLINICAL STAGES IA/IIA HODGKIN LYMPHOMA AND A 'NEGATIVE' 18FDG-PET SCAN AFTER 3 CYCLES ABVD

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In limited stage HL abbreviated chemotherapy (CT) followed by

involved field radiotherapy (IFRT) is the current standard of care but some patients (pts) may be cured by CT alone. 18FDG-PET provides an opportunity to identify pts with an excellent prognosis after CT but the impact of treatment de-escalation on disease control requires careful assessment. Here we present the 3rd interim analysis of the RAPID trial evaluating a PET based, response adapted approach in pts with stages IA and IIA HL. After 3 cycles ABVD a PET scan is performed and if this is reported -ve (score 1 or 2 on a 5 point scale) following central review at the Core Lab, pts are randomised between IFRT and no further treatment. Those with a 'positive' (+ve) PET scan (score 3, 4 or 5) have a 4th cycle ABVD and IFRT. When 400 PET-ve pts have been randomised the trial is powered to exclude ≥7% difference in PFS. At the time of datalock in 01/10, 548 pts (291 male, 257 female; median age 35 yrs) had been registered. Following 3 cycles ABVD, 500 have had a PET scan allocated a score of 1 (n=275, 55%), 2 (n=103, 20.6%), 3 (n=71, 14.2%), 4 (n=29, 5.8%) or 5 (n=22, 4.4%) giving an overall PET-ve rate of 75.6%. 373 PET-ve pts have been randomised to receive IFRT (n=186, 49.9%) or no further treatment (n=187, 50.1%). 5 pts have not been randomised (pt choice, 2; clinician choice, 2; error, 1). After a median 25.6 months from randomisation, 349 of 373 (94%) pts are alive and progression free, 19 (5%) have progressed and 5 (1.5%) have died (HL, 1; other 4) giving a combined 3 year progression-free survival of 93% and overall survival of 98.5%. This 3rd interim analysis confirms earlier findings of a PET+ve rate after 3 cycles ABVD at the upper end of the expected range, a low event rate after short follow-up and no reason identified by an Independent Data Monitoring Committee to prematurely close the trial. The recruitment target of 600 to deliver 400 PET-ve pts for randomisation will be achieved end 07/10.

Advanced Stages

C060

HODGKIN'S DISEASE AND HIV INFECTION (HD-HIV): PROGNOSTIC FACTORS IN 596 PATIENTS (PTS) WITHIN THE EUROPEAN GROUP FOR THE STUDY OF HIV AND TUMOURS (GECAT)

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Background. Hodgkin's disease (HD) is the most common non-AIDS defining tumour diagnosed in HIV setting. The introduction of highly active antiretroviral therapy (HAART) has opened a new prospective in the treatment of pts with HD-HIV as the better control of the underlying HIV infection allows the use of more aggressive chemotherapy regimens, including high dose chemotherapy. However, up to now prognostic factors on overall survival (OS) or time to treatment failure (TTF) have not been identified yet. *Methods.* in order to identify prognostic factors, we analyze data on 596 pts with HD-HIV diagnosed and treated in 90 different Institution from 6 European countries from October 1983 to March 2010. All factors were analyzed for OS and TTF. *Results.* 86% of pts were male and the median CD4 cell count was 224/ L (range 3-1274); 52% of pts had mixed cellularity subtype, stages III-IV were diagnosed in 72% of cases and 55% of pts had extranodal involvement (bone marrow 35%, spleen 21%, liver 14%). Table 1 summarizes the results of multivariate analysis. *Conclusion.* We identified a new "European Score" (IPS>2 and CD4 cell count <200/ L) for HD-HIV able to predict different outcomes in these patients. This score should be considered for future prospective studies.

Table 1.

Overall Survival		
IPS < 2	1	
IPS > 2	2.33 (1.61-3.39)	P<0.0001
CD4 >=200	1	
CD4 < 200	1.63 (1.16-2.29)	P=0.005
Time to Treatment Failure		
IPS < 2	1	
IPS > 2	1.57 (1.09-2.26)	P=0.02
CD4 >= 200	1	
CD4 < 200	1.43 (1.02-2.01)	P=0.04
European Score for Survival		
0	1	
1	2.06 (1.40 - 3.02)	
2	3.08 (2.13 - 4.45)	P<0.001
European Score Time to Treatment Failure		
0	1	
1	1.64 (1.17 - 2.30)	
2	2.31 (1.66 - 3.20)	P<0.001

C061

EARLY INTERIM FDG-PET DURING INTESIFIED BEACOPP THERAPY FOR ADVANCED-STAGE HODGKIN DISEASE SHOWS A LOWER POSITIVE PREDICTIVE VALUE THAN DURING ABVD

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Background. FDG-PET performed early during standard ABVD chemotherapy for Hodgkin's disease (HD) is a powerful prognostic tool (Hutchings: Blood 2006, Gallamini: Haematologica 2006). So far, few data have been published on the role of early FDG-PET in HD patients treated with BEACOPP. *Aims.* 44 advanced-stage HD patients admitted to 8 Italian hematological institutions were considered in a retrospective study to examine the predictive role on treatment outcome of early interim FDG–PET in HD patients treated with BEACOPP (4 escalated + 4 baseline cycles). *Patients.* The mean age was 34.6 years (18-60); advanced disease (stages IIB-IVB) was present in 41, and stage IIA with adverse prognostic factor (>3 nodal sites involved, sub-diaphragmatic presentation, bulky disease, ESR >40) in 2 patients. Bulky disease and extra nodal sites were recorded in 20 and 18 patients, respectively. *Methods.* All patients were staged at baseline, after 2 BEACOPP courses, at the end of treatment by FDG-PET scan (PET-0, PET-2, PET-8, respectively). The mean interval between the end of the second BEACOPP course and PET-2 was 13 days. The threshold for positive PET scan was an FDG-uptake higher than the background. At the end of chemotherapy in 19/20 patients with bulky disease consolidation radiotherapy was given. Two patients switched to ABVD therapy due to toxicity. No treatment change depending on PET-2 result was allowed, except in case of overt progression. *Results.* the mean follow-up was 48 months (17-89). 39/42 patients attained CR (93%), while 3 were chemoresistant and showed disease progression during therapy. Six patients relapsed, 7 to 30.6 months after CR. The Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for treatment failure were 30% and 83%, respectively. The sensitivity, specificity of PET-2 were 44% and 91%, respectively. The 3-y Failure-Free Survival probability for PET-2 negative and for PET-2 positive patients were 86% and 70%, respectively. *Conclusions.* With the caution due to the relatively small number of patients, the results show lower sensitivity and PPV during BEACOPP compared to ABVD regimen; by contrast, specificity and NPV are similar. Moreover these data point toward inadequacy of traditional criteria for interim-PET interpretation during BEACOPP treatment.

C062

INTENSIFIED ABVD FOR NEWLY DIAGNOSED PATIENTS WITH ADVANCED-STAGE CLASSICAL HODGKIN'S LYMPHOMA

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Background. Definition of an optimal risk–adapted strategy for Hodgkin's lymphoma is still under discussion. We previously reported results of a prospective study evaluating dose-dense (dd-ABVD) and dose-dense/dose-intense (dd-di-ABVD) variants of ABVD regimen (Blood, Nov2009;114:715). Here we present the updated data for the high-risk (GHLSG criteria) subset of patients. Strategy concepts of dd-di-ABVD: 1) shorter therapy: 6 cycles delivered in only 16 weeks; 2) time-intensification: shortening of intercycle period from 28 to 21 days; 3) dose-escalation of adriamycin from 50 to 70 mg/m^2 in cycles 1-4 (cumulative 380mg/m^2); 4) primary prophylaxis with G-CSF; 5) the therapy program was driven by interim-FDG-PET; normalisation of PET at the end of the 2nd cycle was an indicator of early-CR, while the persistence of PET+ lesion(s) at the end of the 4th cycle indicated failure and consequently the treatment was shifted to a salvage therapy; 6) consolidation radiotherapy was strictly restricted to bone lesions. *Patients.* From June 2004, seventy advanced-stage HL patients (homogeneous annual accrual) were enrolled in the study (minimum follow up=12 months). Main presentation features were: stage IV(56%) stage III(24%) stage II(20%), bulky(49%); Extranodal(66%) IPI3+(43%), B-symptoms(71%), high-LDH(44%). *Results.* (and comparison with historical advanced/high risk HL patients treated with standard ABVD). *Response.* early-CR 91%(dd-di-ABVD); CR 99%(dd-di-ABVD)versus79%(standard-ABVD) p=0.001. Kaplan-Meyer cumulative survival rates: EFS 94%(dd-di-ABVD)versus62%(standard-ABVD) log-rank=16.26 P=0.0001; OS 99%(dd-di-ABVD)versus80%(standard-ABVD) log-rank=6.24 P=0.004. *Toxicity.* Both hematologic and extra-hematologic toxicity was, overall, mild-to moderate and comparable to standard-ABVD. Cardiac and pulmonary functions were constantly monitored during therapy and the follow up. No G3-4 events of early and late cardiotoxicity were seen. Three events of pulmonary toxicity (G3) were successfully treated with support. Planned RELATIVE DOSE INTENSITY(RDI): standard-ABVD=1; dd-di-ABVD: adriamycin=1.69; bleomycin=1.33; vinblastine=1.33; dacarbazine=1.33. Median delivered-RDI: standard-ABVD: adriamycin=0.81; bleomycin=0.79; vinblastine=0.83 dd-di-ABVD: adriamycin=1.54; bleomycin=1.20; vinblastine=1.21. *Conclusions.* Intensification of ABVD is clinically feasible and it leads to an increase of delivered RDI over planned standard-ABVD (greaterthan50% for adriamycin and ~20% for the remaining drugs); dd-di-ABVD shows higher CR, EFS and OS rates as compared to consolidated standard results. The toxicity profile of intensified ABVD is acceptable. No unexpected cardiac and pulmonary toxicity emerged. Based on these results a randomized prospective comparison of intensified ABVD versus standard-ABVD and/or escalated-BEACOPP seems justified.

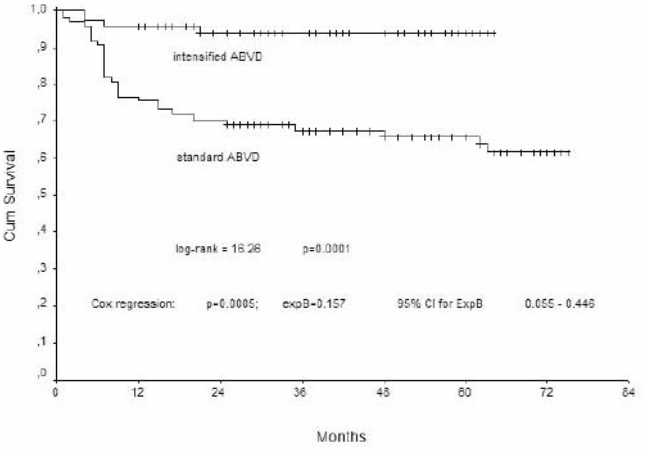

Figure. Event free survival in newly diagnosed advanced-stage HL patients: comparison between intensified vs. standard ABVD.

C063

BEACOPP IS SUPERIOR TO ABVD IN PATIENTS WITH ADVANCED HODGKIN LYMPHOMA AND HIGH TUMOR BURDEN

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Purpose. A comparative evaluation of curative potential of ABVD and BEACOPP based on initial tumor burden. *Experimental Design.* Less than

a complete remission at the end of treatment and relapse occurring within 12 months thereafter were assumed to be clinical expressions of chemoresistance. The tumor burden was calculated from the measurements of all the lesions documented by staging computed tomography and normalized to body surface area to give the relative tumor burden (rTB). Using logistic regression analysis, the relationship between initial rTB, chemoresistance and chemotherapy regimen administered was studied in 222 patients enrolled in two similar randomized trials in that compared BEACOPP with ABVD (HD2000 and IIL/GITIL trial). *Results.* The median rTB volumes were 157.9 ccm/sqm in the 115 patients treated with ABVD vs. 154.6 ccm/sqm in the 107 treated with BEACOPP and the distribution of the volumes was identical in the two groups. The rTB was confirmed as the best predictor of early treatment failures (22 less than complete responses plus 21 early relapses). For the same rTB the risk of chemoresistance to BEACOPP was about half that of chemoresistance to ABVD or, for a given risk of chemoresistance, BEACOPP cured patients with a rTB 89.1 ccm/sqm greater than did ABVD (i.e., more than 50% of the median tumor load of advanced-stage patients). *Conclusions.* In patients with advanced HL, BEACOPP has proven a higher ability compared to ABVD to overcome the potential chemoresistance related to the initial tumor mass.

P064

ADVANCED HODGKIN'S LYMPHOMA: RESULTS IN 216 PATIENTS TREATED WITH ABVD IN BRAZIL

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The outcome of Hodgkin's lymphoma (HL) has markedly improved over the past few decades, making HL one of the human cancers with greater chances of cure. However, data about treatment outcomes in developing countries are scarce. From 1996 to 2005, 370 consecutive patients with HL were treated in three public institutions in Rio de Janeiro. A total of 216 patients who presented with advanced stage (IIB-IV) were selected for the present analysis. Patients with advanced disease were treated with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine), complemented or not by radiation therapy at the physician's discretion. The median follow-up of survivors was 6.3 years (1-11.8). Fifteen patients died during front-line treatment. The complete remission rate was 80%. The 5-year progression-free survival (PFS) and the 5-year overall survival (OS) were 69% and 83%, respectively. The 5-year PFS in low-risk and high-risk patients were 81% and 62% (P=0.003), respectively. The 5-year OS in low-risk and high-risk International Prognostic Score patients were 89% and 78% (P=0.02), respectively. Complete remission rates and survival probabilities were equivalent to those achieved with the ABVD regimen at large medical centers worldwide, and they can be considered excellent for a malignant disease. This series of 216 patients mirrors the reality of treatment of advanced-stage HL in the public setting in Brazil, without the interference of selection criteria. Since Brazil is a large country, with substantial inter-regional heterogeneity, a nationwide registry of HL patients is currently being implemented.

P065

AHOPCA LH-2004, RESULTS OF HEPATOMEGALY AND HEPATIC INFILTRATION IN PEDIATRIC HIGH RISK PATIENTS WITH HODGKIN LYMPHOMA IN CENTRAL AMERICA AND DOMINCAN REPUBLIC AHOPCA LH 2004

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Purpose. Childhood Hodgkin lymphoma is highly curable. Unfortunately event free survival (EFS) in developing countries is still around 50%. AHOPCA is a collaborative group providing protocol driven therapy for children with malignant disorders in Central America and the Dominican Republic. We report here an analysis of significance of hepatic involvement as hepatomegally and/or liver metastasis patients with stages, IIIB and IV were treated with a Modified Stanford V (doxorubicin 25mg/m^2 and vinblastine 6 mg/m^2 weeks 1,3,5,7,9 and 11; vincristine 1.4 mg/m^2 and bleomycin 6 units/m^2 weeks 2,4,6,8,10 and 12; cyclophosphamide 600 mg/m^2 weeks 1,5 and 9; etoposide 60 mg/m^2 daily for 2 days weeks 3,7 and 11; prednisone 40/m^2 given every other day weeks 1 through 10 tapering dose over weeks 11 and 12; radiotherapy, involved fields, given at 20Gy for patients in CR after chemotherapy and 25Gy for those in PR. *Results.* 143 patients stage III or stage IV were evaluated for liver involvement. For analysis the patients were divided into two groups: Group O: no liver involvement and Group 1 liver involvement. Of these patients 99 had no liver involvement, 24 had hepatomegaly, 12 metastasis and 8 both. At last follow up 85 patients are alive and 58 have had an event: death, abandonment of therapy or lost to follow-up less than a year from end of therapy. The EFS at 20 months of 65% is the same for both groups. By 29 months the survival of group 1 is 25% but the survival of group 0 is still >50%. These differences have not yet reached statistical significance but there is divergence of the curves beginning at 20 months. *Conclusion.* Our data suggest that in the setting of a low income country and the modified Standford V chemotherapy, liver involvement with HL may be predictive of poor outcome. Further follow-up of these patients is required to confirm this observation.

P066

A RISK-ADAPTED, RESPONSE-BASED THERAPEUTIC REGIMEN USING A MODIFIED STANFORD V APPROACH FOR THE TREATMENT OF CHILDREN WITH HIGH RISK HODGKIN LYMPHOMA, AHOPCA LH 2004, A THERAPEUTIC REGIMEN FROM THE CENTRAL AMERICA AND DOMINICAN REPUBLIC ASSOCIATION OF PEDIATRIC ONCOLOGY

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The Asociación de Hemato-Oncología Pediátrica de Centro América (AHOPCA) is a collaborative group that designs therapeutic guidelines (protocols) for the treatment of selected malignant disorders in Central America and the Dominican Republic. The purpose of the protocol (AHOPCA LH 2004) was to provide proven effective therapy that would improve survival, decrease toxicity and decrease abandonment of therapy in this group of patients. *Methods.* All newly diagnosed biopsy proven HL patients Ann Arbor stages IIB, IIIB and IV, that presented within the

seven AHOPCA centers between April 2004 and April 2009 were eligible. Treatment consisted of a modified Stanford V regimen with dose-equivalent cyclophosphamide substituting for nitrogen mustard since the latter was unavailable in Central America. Involved field radiation therapy (IFRT) was reduced from the original 35 Gy. Patients that had achieved a complete response at that point received 20 Gy IFRT, patients with less than a complete response received 25 Gy. Trimethoprim and acyclovir prophylaxis was given to all patients. Patient data was collected and entered prospectively in POND, Toxicities were recorded according to CTCAE 3.0. *Results.* 221 patients were enrolled of which 206 were evaluable. Male subjects predominated (79%) with a median age of 10 years (2-19). The risk distribution consisted of 49 (23%) stage IIB, 100 (48%) stage IIIB, 4 (2%) stage IVA and 50 (24%) stage IVB. Histological classification of HL was: nodular sclerosis 45%, mixed cellularity 42%, lymphocyte predominant 5%, lymphocyte depleted 2% and classical not otherwise specified 6%. The most important grade 3 and 4 toxicities were hematological (75%) and there were two grade 5 toxicities, one infectious and one pulmonary. EFS (±SE) at 3 years was 55.4 % (±4.4), considering abandonment of therapy as an event, and the overall survival (±SE) was 75.1% (±4.2). Abandonment of therapy was 14.6% for the whole cohort. *Conclusions.* Our modified Stanford V is a well tolerated regimen with minimal toxicities that does not require growth factor support. However, the EFS of patients was less than expected for the group as a whole, (55.4%), and the abandonment rate still unacceptable despite the ease of administration.

P067

TREATMENT OF ADVANCED STAGES OF HODGKIN LYMPHOMA IN THE CZECH REPUBLIC. SIXTEEN YEARS OF COOPERATION WITH GHSG (1995–2010)

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Overall 647 pts (87% randomized) from University Hospital Kralovske Vinohrady, Prague and from University Hospital Brno were recruited into prospective multicentric trials of GHSG (HD7-HD15 studies). 304 (46%) were in advanced stages of HL. HD9: 35 (12%), HD12: 83 (27%), HD15: 186 (61%), median follow-up 13, 9 and 5 years. Pts evaluated in our study were treated either with chemotherapy BEACOPPesc or timely intensified BEACOPP14, overall 288 pts (HD9C, HD12 and HD15). Median age 30 years. Results of HD9C, HD12, DH15 study analyses - 30. 6. 2010 update. 100% (n=19), 97% (n=81) and 95% (n=176) pts achieved complete remission (CR) at the end of therapy. 84 %, 49% and 16% pts were irradiated in the above mentioned studies. Progressions within 3 months after treatment completion: no in HD9C study, one in HD12 study and 8 (4.3%) in HD15 study. Relapses were observed in 8 pts (4.3%) in HD15 study including early relapse (3-12 m after therapy) in 2 pts and late relapse (>1 year) in 6 pts. More than half of progressed/relapsed HD15 pts were not irradiated after chemotherapy. Positive predictive and negative value of PET at the end of therapy was 33% and 95%. 2 second cancers occured in every study: histiocytosis and lung carcinoma in HD9C, renal and pharyngeal carcinoma in HD12, two AML/MDS in HD15 study. Mortality: one patient died one year after therapy due to histiocytosis, the second patient died 11 years after therapy due to cardiac failure at the age of 45 years in HD9C study. 3 pts died in HD12 study: one young patient with non-compliance – she died due to acute treatment toxicity, another patient with advanced disseminated lymphoma due to HL progression and the third patient due to pharyngeal carcinoma (hard smoker). Overall 7 pts died within the HD 15 study including 4 due to HL progression, 2 due to acute treatment toxicity and the third due AML/MDS. HD9C: 89% (n=17), HD12: 96% (n=80), HD15 96% (n=179) pts are currently in CR. Statistical evaluation of our results is included in regular GHSG analyses.

P068

LONG TERM RESULTS OF STANFORD V REGIMEN AND HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) IN 59 PATIENTS (PTS) WITH HD AND HIV INFECTION (HD-HIV)

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Background. The introduction of HAART has significantly improved the outcome of pts with HD-HIV. However there are no data on the long term follow-up of HD-HIV pts treated with conventional chemotherapy (CT) regimens. In 2002, we reported the results of a prospective phase II study with the intensive 12-week CT with adjuvant radiotherapy (Stanford V) and concomitant HAART in 59 pts (Spina *et al.* Blood 2002;100:1984-1988). *Methods.* To analyze the long term outcome of patients included in the Stanford V and HAART protocol. *Results.* The median follow-up is 67months (range 3-156 months The 5-yr overall survival (OS), freedom from progression (FFP), disease free survival and event free survival are 54%, 52%, 60% and 37%, respectively. The 5-year OS is significantly different in pts with an international prognostic score (IPS) >2 in comparison to that of pts with an IPS <3 (84% vs 36%, P=0.0005). Similarly, the percentages of FFP at 5 years in these groups are 72% and 45% (P=0.03). *Conclusions.* Our data confirm the long term efficacy of Stanford V regimen in combination with HAART in HD-HIV. However, Stanford V is significantly less effective in pts with IPS>2 and therefore new strategies be tested in this setting.

Supported by AIRC and ISS grants.

P069

VEBEP REGIMEN AND HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) IN PATIENTS (PTS) WITH HD AND HIV INFECTION (HD-HIV): FINAL RESULTS OF A PHASE II STUDY OF THE ITALIAN COOPERATIVE GROUP ON AIDS AND TUMORS (GICAT) STUDY

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Background. The outcome of pts with HD-HIV is still poor, because the duration of complete remission (CR) is generally short. To improve the prognosis of HD-HIV, a feasibility study with the VEBEP regimen and HAART was started in previously untreated HD-HIV pts. *Methods.* CT included epirubicin 30 mg/m^2/day (days 1-3), cyclophosphamide 1000 mg/m^2 (day 1), vinorelbine 25 mg/m^2 (day 1), bleomycin 10 mg/m^2 (day 3) and prednisone 100 mg/m^2/day (days 1-3). HAART was given concomitantly to CT. *Results.* From September 2001 to December 2008, 73 pts have been enrolled. The median age was 41 yrs. The median CD4$^+$ cell count was 248/mm^3 and 51% of pts had a detectable HIV viral load. Stage III-IV was present in 50/71 (70%) pts. Histologic subtypes were: MC 70%, NS 20%, LD 4%, LP 2%, unknown 4%. Four toxic deaths (5%) were observed (septic shock, PCP, hepatic failure and pneumonia during neutropenia). An absolute neutrophil count <500 was noted in 60% of pts. Grade 3-4 anemia was observed in 38% of pts and severe thrombocytopenia in 22% of pts. Twenty-two per cent of pts had febrile neutropenia with 19 documented infections in 16 pts (4 varicella, 4 bacterial pneumonia, 3 bacterial sepsis, 2 PCP, 1 cerebral toxoplasmosis, 1 esophageal candidiasis, 1 HBV reactivation, 1 HCV reactivation, 1 prostatitis, 1 salmonellosis). CR was obtained in 49/73 pts (67%) and PR in 8/73 pts (11%). With a median follow up of 40 months (range 2-106), only 5 of CR pts have relapsed. The 3-yr OS and TTF at 24 months were 66% and 63%, respectively. An IPS greater than 2 (HR 2.87, 95%CI 1.08-7.63, P=0.03) and a ECOG-PS greater than 1 (HR 2.79, 95%CI 1.21-6.44, P=0.02) were significantly associated with a higher risk of death. *Conclusions.* Our data demonstrate that VEBEP regimen in combination with HAART is feasible and active in pts with HD-HIV. As observed in HD of the general population, the IPS is able to stratify patients with different outcome.

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P070

EFFICIENCY AND COMPLICATIONS OF EACOPP-14 AT PATIENTS WITH ADVANCED STAGES OF HODGKIN DISEASE

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The purpose. To estimate the efficiency programm EACOPP-14±radiotherapy (RT) and to analyse the frequency of the complications which can take place during treatment. *Materials and methods.* we identified 33 newly diagnosed patients with advanced stages of Hodgkin disease (HD). All patients received 6 cycles of EACOPP-14 chemotherapy (etoposide, adriablastin, cyclophosphamide, natulan, vincristine, prednison + G-CSF from 9 to 13 days of cycle). The cycle repeates q 15 days. The efficiency of treatment was estimated after 6 cycles of EACOPP-14 and prior to the beginning of RT. *Results.* After 6 cycles of EACOPP-14 complete remission had 22(67%) of patients (pts), partial remission – 10(30%) pts, progression of disease had only 1(3%) pts. Among infectious complications were most often diagnosed mucositis and pneumonia – 10(30,3%) pts and 8(24,3%) pts respectively. Infections of the upper respiratory tract and adenovirus diseases had 7(21,2%) pts. Skin and soft tissue infections (including herpes) had 5(15%) pts. Infections of the urinary tract and enteropathy had 1(3%) pts and 2(6%) pts respectively. Thromboses had 1(3%) pts, anaemia (grade III-IV) had 21(63,6%) pts, neutropenia (grade III-IV) had 15(45,5%) pts. Prolongation of intervals more than 3 days because of treatment complications is ascertained after 31 of 196 cycles (15,8%). *Conclusions.* EACOPP-14 programm for advanced stages of HD group patients is effective treatment with high frequency of complete and partial remissions. Among infectious complications most often met mucositis and pneumonia. The special attention is deserved by high frequency of development anaemia and neutropenia grade III-IV.

P071

ABVD WITH OR WITHOUT RADIOTHERAPY IN THE TREATMENT OF ADVANCED STAGE HODGKIN DISEASE. ONE CENTER EXPERIENCE

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Introduction. The treatment of advanced stage Hodgkin disease (HD) remains a challenge. The introduction of BEACOPP seems to offer a better response rate in this patient group, although bearing increased toxicity. We retrospectively evaluated the efficacy of ABVD (Adriamycin, Bleomycin, Vinblastine, Deticene) combined with radiotherapy (RT) in the treatment of advanced stage HD, according to the German Hodgkin Study Group (GHSG) criteria. *Methods.* Seventy-six patients with median age 32 years (range, 15-78) and median follow-up 45 months (range, 5-133) were evaluated. Forty-seven patients had bulky mediastinal and 40 had extranodal disease. Twenty-nine patients (37%) were high risk with ≥4 adverse prognostic factors, according to IPS scoring system, and 47 patients (63%) belonged to the low risk group having 0-3 prognostic factors. Forty-two patients were treated only with 6-8 cycles of ABVD, and the remaining 34 patients received also RT in sites of bulky mediastinal or lymph nodes with diameter ≥5 cm at diagnosis. *Results.* Fifty-eight patients are still in complete response (CR), 22 patients relapsed and were rescued with salvage chemotherapy and 16 of them underwent autologous stem cell transplantation (ASCT). Twelve patients died from disease, while six patients are still alive with disease. The total 5-year disease-free survival (DFS) and overall survival (OS) were 61% and 80%, respectively. Independently of prognostic factors, the group of patients who received only ABVD had 5-year DFS and OS 57% and 77%, respectively, while the group of patients who received additional RT had 5-year DFS 66% and OS 84%. According to the IPS scoring system, the low risk group had 5-year DFS 64% and OS 88% and the high risk group had 5-year DFS 54% and OS 76%. One patient (1%) developed secondary solid tumor and another one patient (1%) developed hematological malignancy. *Discussion.* ABVD with RT can be an effective and well-tolerated therapy for this group of patients, given that relapsed patients can be rescued with ASCT. However high risk patients seems to need a more aggressive therapeutic approach.

P072

2 ESCALATED FOLLOWED BY 6 STANDARD BEACOPP IN ADVANCED STAGE HIGH RISK CLASSICAL HODGKIN'S LYMPHOMA – A SINGLE INSTITUTION EXPERIENCE IN 46 PATIENTS

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Introduction. From 1999 Norwegian guidelines recommend 2 escalated (esc) BEACOPP followed by 6 standard (s) BEACOPP for patients (pts) with advanced stage classical Hodgkin's lymphoma (HL) with an international prognostic score (IPS) ≥4. We evaluated the experience with this treatment recommendation at the Norwegian Radium Hospital. *Results.* 46 pts treated with BEACOPP between June 1999 and December 2008 were identified in the hospital's data base (39 males/7 females, median age 41 (range 18-59) years). IPS was 3 in 10 pts and ≥4 in 36. 35 pts received 8 cycles of BEACOPP, 11 pts 1-6 cycles only, mainly due to toxicity. 38 pts received 2 escBEACOPP, 2 pts did not receive any course of esc BEACOPP. Dose reductions due to toxicity were done in 17 pts, mainly regarding prednisolone (n=11), vincristine (n=6) or bleomycin (n=3). One patient died of toxicity. The overall response rate was 100 %, 11 pts with a partial response received radiotherapy to residual volumes. With a median follow-up of surviving pts of 72 months, PFS and OS at 5 years are 83% (95% CI 72 -95%) and 90% (80-99%), respectively. Hematological toxicity grade III-IV for leukocytes, neutrophils, platelets and hemoglobin was recorded in 86, 80, 34 and 30% of pts after escBEACOPP, and in 74, 74, 19 and 36% of pts after sBEACOPP, respectively ($P<0.05$ for platelets, not significant for other items). Grade III-V infections including febrile neutropenia occurred in 83% of pts, including one death, 3 cases of Pneumocystis jiroveci pneumonia and 6 cases of Herpes zoster. Of note, 11 pts (24%) experienced symptomatic MRI verified aseptic bone necrosis, of whom 3 have had hip replacement surgery after treatment. Other grade III toxicities were venous thrombembolic events in 10 pts, polyneuropathy in 11 pts, and bleomycin induced pulmonary toxicity in 4 pts. *Conclusion.* 2 escBEACOPP followed by 6 sBEACOPP appears highly efficacious in advanced stage high risk HL pts. Due to toxicity, close monitoring of pts is mandatory and dose reductions are frequently necessary. We found an unexpected high incidence of aseptic bone necrosis, possibly related to the high dose of prednisolone.

P073

RESULTS OF TREATMENT OF ADVANCED STAGES OF HODGKIN'S DISEASE WITH BEACOPP – 14

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Introduction. In the presence of adverse clinical (such as rapid onset of the disease, tumor growth by over, compression of the neurovascular bundle, lymphostasis, lymph nodes of atypical localizations, Bulky-disease) or morphological (such as syncytial type of growth, lymphoid depletion) characteristics the outcome of treatment of early stages of Hodgkin's disease with standard programs unsatisfactory. In this regard, we have adopted the program BEACOPP-14 not only for stage IV, but for II, III stages with the above risk factors. *Materials and methods.* From February 2006 to March 2010 treatment with program BEACOPP-14 used in 182 patients with Hodgkin's disease at the age of 16 to 71 years (median age 29.5). The ratio of men and women 1,8. Stage II was at 28.9% of patients, III stage -25%, IV stage -46%. Among the histological types of syncytial type of growth and lymphoid depletion amounted to 62,2%. The patients reseaved from 4 to 8 courses BEACOPP-14 and radiotherapy at a total dose of 30 Gy to residual tumor more than 2 cm. *Results.* Treatment program was completed at 180patients, 2 (1%) patient died during treatment after the sixth course of therapy-resistant pneumonia. 178 (98,8%) patients achieved full remission. In 2 (1%) patients there was noted a progress of the disease after completion of radiotherapy. In 42% patients different infection complications were noted, but severe infections developed only in 10%. Late complications - 1 acute myeloid leukemia with del(11)q(23) 2 years after completion of therapy. *Conclusion.* We obtained good results

when applying BEACOPP-14 in patients with Hodgkin's disease with advanced stages, morphological forms and risk factors (98.8% full remission). The case fatality rate during treatment was 1%.

P074

THROMBOSIS IN PATIENTS WITH ADVANCED STAGES HODGKIN'S DISEASE IN THE TREATMENT OF BEACOPP-14

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Introduction. Thrombosis in patients with Hodgkin's disease were contributed by such factors as compression and extension of the tumor vessels, the appointment of steroids and hormonal contraceptives, trauma (surgery, installation of central venous catheter), infection, congenital genetic anomalies (congenital thrombophilia). *Materials and methods.* We analyzed the thrombotic complications that developed in patients with Hodgkin's disease during treatment BEACOPP-14. From February 2006 to March 2010 treatment with program BEACOPP-14 used in 182 patients with Hodgkin's disease at the age of 16 to 71 years (median age 29.5). The ratio of men and women 1,8. *Results.* Thrombotic complications developed in 9 (4.9%) patients aged 17 to 55 years. Localization of thrombosis: subclavian vein-1, deep vein of lower extremities-1, sagittal sinus-2, abdominal aorta-1. Two patients developed thrombosis before treatment, the cause of thrombosis in them was traumatic - one patient developed thrombosis of the femoral vein following inguinal lymph node biopsy and the second patient developed thrombosis after the installation of a central catheter into the subclavian vein. The remaining 7 patients (3.8% of the total number of patients), thrombosis were developed during an interval between courses of chemotherapy at the end of myelotoxic agranulocytosis. At the same time in 5 patients were identified genetic anomaly (markers of thrombophilia). All patients with thrombosis were female, five of whom are in reproductive age, and therefore received ovarioprotective hormonal contraceptives. Complete lysis of thrombus with restoration of blood flow was achieved without surgical intervention on the background of complex treatment with anticoagulants and desaggregants. *Conclusion.* The analysis of thrombotic complications showed that the frequency of their occurrence in the therapy BEACOPP-14 is low (3,8%). The factors contributing to thrombosis are genetic abnormalities (markers of thrombophilia) and hormonal contraceptives. To prevent thrombosis is necessary to define markers of thrombophilia, espesially in female monitorind the coagulation, timely appointment of anticoagulation therapy.

P075

ROLE OF TOTAL BODY MAGNETIC RESONANCE IN DETECTING SKELETAL INVOLVEMENT IN ADVANCED STAGE HODGKIN LYMPHOMAS

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Introduction. Skeletal localizations are reported in approximately 10-20% of advanced stage malignant lymphomas. Computed tomography (CT) is considered the gold standard for lymphoma staging and evaluation of treatment response; this technique, however, has a limited sensitivity in identifying skeletal localizations. Positron emission tomography (PET) has a higher sensitivity in recognizing bone involvement and represents a diagnostic tool, complementary to CT. Total body magnetic resonance (MR) may represent an option for detection and better characterisation of tumoral bone lesions. We compared MR with conventional imaging procedures in the evaluation of Hodgkin lymphoma (HL) patients with suspected skeletal involvement. *Patients and methods.* In a cohort of 115 consecutive newly diagnosed HL patients (pts), 25,2% of pts presented in stage IV; 16 pts (14%) showed skeletal involvement. Nine pts underwent MR in addiction to standard imaging techniques (CT and PET). Total body MR was performed with a body coil (1.5 Tesla) and images were obtained by using fast spin-echo short time inversion recovery and spin-echo single-shot sequences diffusion weighted. In 6 pts MR was performed at diagnosis and in 7 cases as evaluation after treatment, for a total of 13 scans. MR images were compared with those obtained from conventional imaging performed at the same time. *Results.* When performed at diagnosis MR and PET results were concordant, documenting skeletal involvement in all cases, even if MR scans detected more osseous localizations than PET. CT scans didn't evidence any skeletal lesions in 5/6 cases. Seven MR were performed for evaluation after treatment. In 6/7 cases MR scans confirmed PET results. In one case MR and PET results were discordant and PET failed to detect skeletal progression. *Discussion.* These data suggest that total body MR can be useful in the management of Hodgkin lymphoma pts with suspected skeletal involvement, without additional radiation exposure. In the described group CT failed to evidence skeletal localizations in the majority of cases, resulting in inappropriate definition of disease extent at diagnosis. PET is often concordant with total body MR, but detects a lower number of bone lesions.

P076

EXTRANODAL INVOLVEMENT AS PROGNOSTIC FACTOR IN HODGKIN'S LYMPHOMA

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Background. Hodgkin's lymphoma (HL) is predominantly a nodal disease, with extranodal (EN) involvement being uncommon. Despite a high overall cure rate, about one third of patients (pts) with advanced disease have early relapses. Identification of HL pts who are destined to have poor response to treatment by defining initial prognostic parameters, might contribute individualization of treatment and tailoring more effective therapeutic modality. *Aims.* To analyze the prognostic value of EN involvement in advanced HL pts in order to determine optimal initial prognostic model. *Methods.* We examined group of 50 pts with EN disease treated with ABVD regimen from 1997- 2004, at diagnosis. The median follow-up was 7 years. Their significance was evaluated according to the response to treatment (EFS) and survival period (OS). It was correlated with International Prognostic Score (IPS), bulky mass, 3 or more sites involvement, elevated sedimentation rate (ESR>50). *Results.* The distribution of EN disease was: 28 pts had bone marrow infiltration, the lungs in 16 pts, the liver in 13 pts and central nervous system 2. EN two or more localization had 19 pts. The IPS>2 had 36 and bulky disease 24 pts. The EN two or more sites had adverse effect on OS (25% vs 68% for pts without EN, P<.01) and on EFS (31% vs 83%, P<.05). Patients with bulky disease had significantly shorter OS (34% vs 69%, P<.05) as well as EFS (45% vs 80%, P<.05). There was a positive correlation between EN disease and ESR>50 (P=.01). Pts with IPS>2 had shorter OS but it was not significant P=.07. There was no significant correlation with other examined features. Cox's multivariate model revealed EN two or more localizations as a significant independent prognostic factor both for OS and EFS P=.01, P=.02 respectively and bulky disease for OS P=.02. *Conclusions.* Advanced HL pts with EN two or more localization and bulky disease are at higher risk of treatment failure and might be eligible for more effective treatment approach.

P077

EARLY CHEMOTHERAPY INTENSIFICATION WITH BEACOPP IN HIGH-RISK, INTERIM-PET POSITIVE, ADVANCED-STAGE, ABVD-TREATED HODGKIN LYMPHOMA PATIENTS

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Background. Early Interim FDG-PET (PET) performed after two ABVD courses (PET2) is the most reliable prognosticator in advanced-stage, ABVD-treated Hodgkin Lymphoma (AS-HL) patients (p.). We evaluated retrospectively the overall outcome of a cohort of ABVD treated AS-HL p. in which chemotherapy was intensified with BEACOPP in PET2 positive (PET2+) p. *Methods.* From January 2006 to December 2007 214 newly diagnosed HL p. admitted to 8 Italian and 1 American centers were

treated with ABVD x 2 courses. PET2 was performed afterwards: PET2+ p. were treated with BEACOPP, 4 escalated + 4 baseline courses, followed by consolidation RxT on bulky disease (CRxT). PET2- p. were treated with further 4 ABVD courses, and CRxT. *Results.* During the enrolment time 212 p. were consecutively admitted in the above Institutions: 52/212 (23%) were excluded from this treatment because of co-morbidity (8), PET not done (16) other therapy/protocol (7), psychiatric disorder (4), other (1). Prognostic factors were well-balanced between 27 PET2+ and 135 PET2- p. (P=0.14-0.89). All PET2 scans underwent central review (CREw) according to a 5-point semiquantitative score (Barrington 2010). In 152/162 patients CREw confirmed the PET2 interpretation of the local PET center (LOPc). Five p. with a PET2- by LOPc, reclassified as PET2+, showed treatment failure after a median of 1.7 months after ABVD chemotherapy end. In 3 p. a PET2+ by LOPc was redefined as PET2- by CREw: 2 were treated with BEACOPP, 1 with ABVD for medical decision: they are all in CCR 22.6 months (20-22.9) after diagnosis. After a median follow up of 26 (10-44) months the 2-year failure free survival (FFS) and overall survival (OS) for the entire cohort of 162 p. were 88.5 % and 98%; 64% and 96% for PET2+, 92.5% and 98% for PET2- p. In the 152 p. in which PET2 scans were reviewed the 2-y FFS was 91.35%, 96.2% for PET2-, 60.5% for PET2+ p. HR 14.26; P<0.00001. Conclusions: PET response-adapted treatment outcome in this retrospective cohort is comparable with that obtained with front-line BEACOPP chemotherapy for all AS- HL p., with a potentially less toxic regimen for most of them.

P078

THE PROGNOSTIC RELEVANCE OF TUMOR ASSOCIATED MACROPHAGES IN ADVANCED STAGE CLASSICAL HODGKIN'S LYMPHOMA

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Background. The presence of tumor associated macrophages in many tumors which was once thought to be a manifestation of an immune response against the tumor now is associated with a poor prognosis. Despite advances in Hodgkin's lymphoma (HL) treatment, approximately 20% of patients (pts) still die from progressive disease. Distinguishing reliable prognostic biomarkers might contribute initially better selection of a drug resistant HL pts for a more effective therapeutical approach. *Aims.* To analyze the prognostic value of tumor associated macrophages in advanced HL pts in order to determine optimal initial prognostic model. *Methods.* In a group of 52 advanced HL pts treated with ABVD regimen from 1997- 2005, we analyzed the prognostic relevance of tumor associated macrophages identified by a CD68 antibody in the immunohistochemical analysis, on lymph nodes tissue sections, at diagnosis. The number of CD68 positive tumor associated macrophages was analyzed on 10 different high power microscopy fields (HPF, ×400) and scored (0-<5%=1, 5-25%=2, >25%=3). The median follow-up was 7 years (yrs). Their significance was evaluated according to the response to treatment (EFS) and survival period (OS) and correlated with International Prognostic Score (IPS), extranodal localization, bulky mass, >3 sites involvement, ESR >50. *Results.* The OS rate was 62%. Patients with an increased number of tumor associated macrophages (CD68+>25%) had worse OS, 45%, compared to those with lower (CD68+<25%), OS 76% (log rank P<0.05). There was no significant correlation with other clinical examined features. Cox's multivariate model revealed that increased number of tumor associated macrophages behave as independent prognostic factor for survival (P=.01). *Conclusions.* Patients with high CD68+ tumor associated macrophages are at a higher risk of treatment failure and therefore could be eligible for more intensive initial therapeutic approach.

P079

LONG TERM FOLLOW-UP OF ADVANCED HODGKIN LYMPHOMA TREATED WITH BEACOPP REGIMEN - A SINGLE INSTITUTION EXPERIENCE

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Aim. The purpose of this trial of Serbian Lymphoma Study Group was to investigate the efficacy of a three different subtypes of BEACOPP regimen in the treatment of advanced stage Hodgkin's disease (HD). *Patients and methods.* From January 2002 to December 2007, 44 previously untreated patients who had newly diagnosed Hodgkin's disease in stage II with risk factors, III and IV were randomly assigned to receive eight cycles of escalated BEACOPP (14 patients) or four escalated plus four standard courses (B/E) (17 patients), or eight standard BEACOPP (13 patients). After eight chemotherapy cycles, initial bulky and residual disease is irradiated. *Results.* There were 32 males and 12 females divided to three groups according to age (up to 30 years, 30-45 years, 45-60 years; 27, 11, 6 patients respectively). Patient's characteristics were: 11.4% had bulky disease (>7 cm), 10 patients were in stage II, 21 in stage III, and 13 in stage IV. Thirty two patients (72.7%) achieved a complete response and 9.1% partial response. No significant difference in overall response rate was observed between patients with different treatment approach, clinical stage, LDH level and bulky disease. With a median follow up period of 60 months, median survival time was 42.7 months in group treated with escalated BEACOPP, 50.2 months in group treated with B/E BEACOPP, and 58.7 months in group treated with standard BEACOPP. There was trend to significantly worse survival in group treated with escalated BEACOPP (P=0.054) in comparison to other two groups. Also, significantly larger number of deaths was observed in group treated with escalated BEACOPP during treatment period (P=0.04). *Conclusion.* The results of the present study demonstrate that the intensive approach was effective therapy for advanced stage HD. We need to stress that baseline and B/E BEACOPP as regimens used in our patients was well tolerated than escalated BEACOPP due to prolonged aplasia.

P080

IDENTIFICATION OF GALECTIN-1 AS PROGNOSTIC BIOMARKER IN YOUNGER PATIENTS WITH ADVANCED STAGE CLASSICAL HODGKIN LYMPHOMA

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Background. In spite of the large number of candidate genes that have been proposed based on gene expression profiling studies in classical Hodgkin lymphoma (cHL), no specific biomarkers have yet been introduced into a routine clinical setting for pre-therapeutic risk assessment. The aim of our analysis was therefore to identify possible prognostic protein markers in advanced stage cHL using a proteomic based strategy. *Methods.* A total of 14 cHL pretreatment tissue samples from younger (<55 yrs), advanced stage (IB, IIB, III and IV) patients, were selected for two-dimensional gel electrophoresis and protein identification by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Patient samples were grouped according to treatment response (unfavorable, N=7 vs. favorable, N=7) and at least 2-fold differentially expressed proteins were identified. Selected proteins were validated using western blotting. Candidate proteins were then further studied in a larger cohort by immunohistochemistry (IHC) using a tissue microarray containing paraffin embedded tumor tissues from patients with advanced stage cHL. Galectin(Gal)-1 expression in the tumour microenvironment was assessed by IHC in 143 cases of advanced cHL and the number of Gal-1+ cell profiles/mm^2 was scored using unbiased counting rules. Clinical data were obtained from clinical records. *Results.* The median age of the 143 patient cohort was 35 yrs (range: 14-86 yrs). The M:F ratio was 1.8. At univariate level, high Gal-1 expression in the tumour microenvironment correlated with poorer event-free survival (EFS) (P=0.049). Furthermore, we found a significant correlation between high Gal-1 expression and the presence of B-symptoms (P=0.03) at diagnosis. Among younger (<61 yrs) advanced stage cHL patients, in addition to a lower EFS, high Gal-1 expression was also associated with poor overall survival (OS) (both P=0.007). At multivariate level, high Gal-1 expression in younger advanced-stage cHL patients retained a significant predictive impact on EFS (P=0.005). In addition, high Gal-1 expression overruled the International Prognostic Score when both parameters were concomitantly tested in a multivariate model. *Conclusions.* In younger (<61 yrs), advanced stage cHL patients, a high expression of Gal-1 in the tumour microenvironment, correlates with the occurrence of B-symptoms at diagnosis and is significantly associated with relapsed-refractory disease.

P081

ABVD AS THE TREATMENT OPTION FOR ADVANCED STAGES OF HODGKIN'S DISEASE IN PATIENTS OLDER THAN 45 YEARS – A SINGLE CENTER 10 YEARS EXPERIENCE

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Background. Advanced age is considered as an unfavourable prognostic factor for Hodgkin's lymphoma (HL). The optimal treatment for these patients is not yet defined, especially for advanced stages. *Aim.* The aim of this study is to asses the effects of ABVD first line treatment on outcome in patients older then 45 years with advanced stages HL, as well to identify risk factors for poor outcome. *Patients and methods.* A retrospective study was performed on 46 HL patients older than 45 years with advanced stages treated with ABVD in the period from June 1997 until June 2007. The patients completed 6-8 cycles of ABVD followed by radiotherapy. *Results.* The median age of the patients was 53.5 (range 45-80). 10 patients (21.7%) were older than 60 yrs. Patients older than 60 yrs had significantly higher rate of comorbidities (90% vs 50%, Fisher's exact test (F)=0.031). 29 patients (63%) achieved complete remission, with significantly lower rate in patients older than 60 yrs (20% vs 75%, F=0.003), IPS≥3 (53% vs 85%, F=0.035), while there was no difference in achieving complete remission regarding presence of large mediastinal tumor (69% vs 61%, F=0.424), extranodal disease (66% vs 58%, P>0.05), bulky disease (66% vs 62%, P>0.05), ESR>50 (60% vs 78%, F=0.268). Patients older than 60 yrs had highly significant shorter both 5 yrs event free survival (log rank=14.798, P<0.01) and 5 yrs overall survival compared to patients 45-60 yrs (log rank=16.593, P<0.01). Patients with IPS ≥3, extranodal disease, bulky disease, ESR>50 had worse event free and overall survival but the statistical significance was not reached, while there was no difference regarding the presence of large mediastinal tumor mass. The multivariate Cox regression analysis identified age >60 yrs as the independent prognostic factor. *Conclusion.* The patients older than 60 yrs with advanced stages HL had worse outcome compared to 45-60 yrs old patients. The prospective clinical trials are needed to define the best therapeutic approach for these patients.

P082

A PHASE I STUDY TO INVESTIGATE DOSE ESCALATION OF DOXORUBICIN IN CYCLES 1-3 OF ABVD CHEMOTHERAPY FOR HODGKIN LYMPHOMA AND TO CORRELATE THIS WITH BLOOD-BORNE BIOMARKERS OF TUMOUR RESPONSE AND TOXICITY

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The GHSG has shown that chemotherapy induced grade III/IV leukopenia correlates strongly with improved freedom from treatment failure suggesting that dose based on Body Surface Area produces variable biological effects. This may explain differences in toxicity, response, PFS and OS, and argues for a more rational approach to dosing. We report interim data from a phase 1 dose escalation cohort study aimed at identifying the maximum tolerated dose (MTD) of doxorubicin within cycles 1-3 ABVD. Dose escalation was performed on a cohort basis (1, 35 mg/m^2; 2, 45 mg/m^2; 3, 55 mg/m^2; 4, 65 mg/m^2) with doxorubicin omitted from later cycles to maintain a cumulative dose between 103%-130% of baseline ABVD. Subjects received PEG-filagrastim (Neulasta, Amgen) after every dose of doxorubicin. BVD was given at standard doses. Dose limiting toxicity (DLT) was defined as grade 4 haematological toxicity lasting ≥5 days, or grade 3 non-haematological (excepting nausea, vomiting), occurring at any time during treatment. MTD was defined as the dose cohort below which ≥3 subjects experienced DLT. At the MTD 6 additional patients were recruited to expand this cohort to 12. Plasma/serum for biomarkers of apoptotic cell death (nucleosomal DNA), and toxicity (M30 and M65) were drawn/stored on days 1,3,8,15,17 and 22 of each escalated cycle. Relevant ELISAs are being performed in a GCLP accredited laboratory and results correlated with outcomes. 24 subjects (13 females; median age 34, range 19-59) were recruited into the study. DLT was reached in cohort 3 with 1 subject experiencing G3 neuropathy, another G3 palmar-plantar erythema (PPE) and a third G3 PPE, G3 neuropathy and an episode of G3 neutropenia-associated infection. All DLTs occurred within the first 3 dose-escalated cycles. Haematological toxicity was manageable with 9 G3/4 events in cohort 2 (none leading to SAE), and 4 events in cohort 3. With 12/24 so far evaluable, PET responses from cohorts 1 and 2, are CR 9, PR 2, PD 1. These data suggest that ABVD may be delivered safely with PEG-filagrastim support at a doxorubicin dose of 45 mg m-2 in cycles 1-3. Analysis of secondary endpoints and correlation with blood-borne biomarkers will be presented.

P083

OUTCOME IN ELDERLY HODGKIN LYMPHOMA (HL): HIGH INCIDENCE OF BLEOMYCIN LUNG TOXICITY (BLT), WHILE FUNCTIONAL STATUS AT DIAGNOSIS AND INITIAL RESPONSE TO THERAPY PREDICT SURVIVAL

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Background. Survival rates for elderly HL patients (>60 years of age) are disproportionately inferior to younger patients. Explanations include treatment-related toxicity and inadequate treatment delivery. Minimal data is available regarding co-morbidity and outcome. *Methods.* Detailed patient and disease characteristics were collected among elderly HL patients treated at 3 Chicago centers (12/99-12/09). Co-morbidities were assessed using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) scale. Patients were also classified as "un-fit" vs "fit" (i.e., preserved activities of daily living (ADLs), <3 grade 3 CIRS-G, no grade 4, and no geriatric syndrome [dementia, delirium, incontinence, falls, neglect/abuse and/or failure to thrive]). *Results.* We identified 56 patients (24F:32M) with a median age of 67 years (61-84). 21% had prior malignancy (most common: breast n=6) at a median of 8.4 years (0-25) before HL (most had received radiation). HL disease characteristics included: B symptoms 56%, PS 2-3 27%, marrow involvement 25%, other/non-marrow extranodal disease 20% (most common: bone n=6 and lung n=5). 64% had advanced-stage disease, of which 61% had an international prognostic score (IPS) ≥4. For co-morbidities, 38% had grade a 3 or 4 CIRS-G in at least 1 category. Additionally, 29% were classified as "not fit" at HL diagnosis, while 16% had a geriatric syndrome. 54/56 patients received chemotherapy; the most common regimens were ABVD (n=34), BCVPP (n=7), and ChlVPP (n=6). The incidence of BLT was 31% with an associated 27% fatality rate. The overall response rate to chemotherapy was 88% (75% complete remission). With 51-month median follow-up (7-120), 4-year PFS and OS for all patients were 36.8% and 57.6%, respectively (early-stage: 61.6% and 80.5%; advanced-stage: 21.7% and 43.4%; P=0.03 and P=0.04, respectively). Additional prognostic factors are shown in Table 1. In multivariate analyses, loss of ADLs (HR 4.44 [0.83-23.71], P<0.08) and <CR to initial therapy (HR 9.32 [1.81-47.92], P=0.008) predicted significantly inferior OS. *Conclusions.* Long-term survival is feasible in elderly HL, however, treatment-related toxicities such as BLT occurs at an unacceptably high rate in this patient population. Further, functional status and initial response appear to signficantly impact survival. More effective and better-tolerated treatments are needed, particularly for advanced-stage patients.

Table 1. Prognostic factors (univariate).

Factor	*EFS*			*OS*		
	HR	95%CI	P	HR	95%CI	P
IPS (continuous)	1.32	1.02-1.72	0.04	1.38	0.98-1.96	0.07
Grade 3-4 CIRS-G (any)	2.05	1.01-4.17	0.048	3.26	1.26-8.42	0.01
PS 2-4	2.46	1.15-5.24	0.02	5.34	2.12-13.45	0.0004
Prior malignancy	3.14	1.47-6.71	0.003	2.40	0.97-5.93	0.057
Geriatric syndrome	3.15	1.39-7.16	0.006	3.10	1.11-8.64	0.03
Hypoalbuminemia	3.45	1.40-8.53	0.007	6.78	1.53-30.10	0.01
Loss of ADL(s)	8.46	2.86-25.01	0.0001	17.80	5.41-58.58	<0.0001
<CR initial therapy	10.79	4.55-25.60	<0.0001	15.83	5.49-45.69	<0.0001

P084

COMPARISON BETWEEN BEACOPP-ESCALATED AND ABVD- INCLUDING CHEMOTHERAPY FOR HODGKIN LYMPHOMA PATIENTS: A SYSTEMATIC REVIEW

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Introduction. To find the optimal treatment with best efficacy and least toxicity is the main challenge in treating Hodgkin lymphoma (HL). Two different international standards to treat intermediate and advanced stage HL exist: the ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) regime and the BEACOPPescalated (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) regime. This review aims to clarify advantages and disadvantages of both treatments. *Methods.* MEDLINE and CENTRAL were systematically searched for randomised controlled trials from 1985 to 2010. Trials comparing treatment with at least 2 cycles BEACOPPescalated versus chemotherapy with at least 4 cycles of ABVD for patients in early-unfavorable or advanced stages HL were included. Trial selection, quality assessment and data extraction were done independently by two review authors. Time-to-event outcomes were analyzed with hazard ratios (HR) and 95% confidence interval (CI) in a fixed effect model. *Results.* A total of 718 references were screened. Four eligible trials with 2255 patients were identified: the HD9 and HD14 trials from Germany, the HD2000 and GSM-HD trials from Italy. All trials reported results for progression free survival (PFS) and overall survival (OS). PFS was statistically significantly longer for BEACOPPescalated: HR was 0.52 (95% CI [0.43, 0.64], I2=0%). OS was statistically significantly longer for BEACOPPescalated: HR was 0.71 (95% CI [0.50, 0.99], I2=0%). However, in a sensitivity OS analysis without the HD9 trial the HR was 0.83 (95% CI [0.50, 1.38]). Two trials report toxicity during treatment: the BEACOPPescalated regime causes statistically significantly more haematological toxicities WHO grad 3-4, infections, alopecia, mucositis and pain than regimens including ABVD. There were differences between both regimens for constipation, nausea and neurologic toxicity. None of the trials provided results regarding infertility or quality of life. *Conclusions.* This systematic review showed a better PFS and suggests a benefit in OS for BEACOPPescalated in comparison to regimens including ABVD. Furthermore, the meta-analysis confirmed the higher haematological toxicity of the BEACOPPescalated regimens. No trial provided results regarding quality of life or infertility. However, 3 trials had a short follow-up. Longer follow-up and the inclusion of the ongoing EORTC 20012 trial should allow a more definitive answer concerning OS.

P085

TREATMENT OF ADVANCED STAGE HODGKIN LYMPHOMA WITH 4 CYCLES OF BEACOPP ESCALATED FOLLOWED BY 4 CYCLES OF BEACOPP BASELINE: LONG-TERM RESULTS FROM A SINGLE CENTRE

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Introduction. HD-12 trial of the GHSG de-escalated therapy of advanced stage of Hodgkin lymphoma (HL) by comparing 8 cycles of escalated BEACOPP with 4 cycles of escalated BEACOPP and 4 cycles of baseline BEACOPP. We evaluate efficacy and toxicity of this schema used in our institusion since 2001. *Patients and methods.* A total 68 patients with newly diagnosed HL – advanced stage were treated with this approach, 57 of them (median age 31 years) with minimal FU of 12 months from the end of therapy were finally evaluated. Initial stage II/III/IV disease was found in 12/29/16 patients, respectively. We analyzed this group of patients for early toxicity, outcome in interim restaging and treatment outcome. *Results.* A total of 54 (95%) patients achieved complete remission. One patient progressed on treatment, one had stable disease. One patient died during treatment. Radiotherapy was given to 10 patients with residual PET positivity. Three patients experienced disease relapse 13/22/22 months after the beginning of the therapy. Relapse or progression occured in only 5 patients (9%). With the median of follow-up (FU) 56 months FFTF for all patiens is 90%, OS is 93 %. *Toxicity.* Preplaned 8 cycles of the therapy completed 49 patients (86%). 5 patients didn't complete treatment due to adverse events (AE), 2 due to non-compliance. Major toxicities were hematologic. The grade 3-4 anemia has occured in 25 patiens (44%), grade 3-4 neutropenia in 50 (88%) and grade 3-4 thrombocytopenia in 22 (39%) patients. G-CSF support in baseline BEACOPP was needed in 36 (63%) patients, 9 patients were hospitalized due to febrile neutropenia. Other examined early AE were aseptic necrosis of the had of femur, venous thrombosis, soft tissue absces, chronic osteomyelitis, peripheral neuropathy, pneumonitis and osteoporosis. During the FU period 1 patient had secondary malignancy, 1 patient myelodysplasia following salvage high-dose chemotherapy with stem cell rescue. *Conclusion.* These data showed that combination of escalated and baseline BEACOPP chemotherapy seems to be effective treatment with acceptable acute toxicity, very promising effectivity. Longer follow-up is needed for evaluating of late toxicity of this regimens.

Relapsed and Refractory

C086

AUTOLOGOUS STEM CELL TRANSPLANTATION FOR ADOLESCENTS AND YOUNG ADULTS WITH RELAPSED OR REFRACTORY HODGKIN LYMPHOMA

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Introduction. Adolescents and young adults (AYAs) with HL represent a unique patient population, facing cancer and the toxicities of therapy during an important, transformative period of their lives. The long term outcomes of AYAs undergoing intensive chemotherapy and autologous stem cell transplantation (ASCT), both medical and psychosocial, have not been well studied. We assessed the outcome of AYAs undergoing ASCT to define treatment outcome, and assemble a cohort in which we can evaluate the effect of treatment for relapsed disease on personal developmental and psychological outcomes. *Patients and Methods.* Between 1988 and 2009, 162 AYAs (median age 25, range 16-30) with relapsed or refractory HL received salvage therapy followed by ASCT at our centre. Patient characteristics: M:F 83:79; advanced stage (IIB-IV) at diagnosis 84%; first progression or relapse: 90%. All patients had complete or partial response to 2-3 cycles salvage chemotherapy (cisplatin-based or mini-BEAM), and underwent bone marrow harvest (n=83) or stem cell mobilization with cyclophosphamide and etoposide (n=79). Intensive therapy: etoposide 60 mg/kg day + melphalan 180 mg/m2; patients with disease bulk >5 cm at relapse received post-ASCT involved field radiation if tissue tolerance allowed. *Results.* To date, 88 of 162 patients have relapsed, and 67 remain alive in CR; 18 (11%) died from treatment related-toxicity (9), second malignancies (4 AML, 2 NHL, 1 lung cancer) or unknown causes (2). Five-year progression-free survival is 42.4% ±4% and 10 year overall survival is 38.4% ±5%; there have been no HL relapses beyond 39 months post-ASCT. *Conclusions.* While highlighting the clear need for improved strategies for disease control for AYAs undergoing ASCT, this analysis has provided a cohort of patients in which to evaluate the long-term impact of intensive therapy on personal and social adjustment, and to identify opportunities for psychosocial intervention and health promotion.

C087

LONG TERM OUTCOME OF HIGH-DOSE SALVAGE THERAPY FOR PATIENTS WITH EARLY STAGE HODGKIN LYMPHOMA (HL) WHO FAILED INITIAL TREATMENT WITH COMBINED MODALITY TREATMENT OR CHEMOTHERAPY ALONE.

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Purpose. We analyzed the outcome of early-stage HL patients with relapsed/refractory disease that underwent salvage high-dose therapy (HDT) and autologous stem cell transplantation (ASCT). *Methods.* From 11/85 to 07/08, 207 patients with relapsed/refractory HL after initial early-stage presentation were treated on 4 consecutive prospective salvage protocols. 137/207 (66%) patients relapsed after complete response (CR) to initial therapy and 70 (34%) were refractory. Of the patients with relapsed HL, 35 (25%) were initially treated with chemotherapy alone (CA) and 102 (75%) with combined modality therapy (CMT). 56 (80%) patients remained refractory after CA and 14 (20%) after CMT. All salvage programs consisted of standard-dose chemotherapy followed by IFRT/accelerated TLI/HDT for radiation-naïve patients or IFRT/HDT if previously irradiated. 14 patients did not proceed to ASCT due to progression of disease or toxicity and were excluded. Overall (OS) and event-free survival (EFS) were analyzed by Kaplan-Meier and Cox regression. Disease-specific survival (DSS) was analyzed by competing risk regression. *Results.* With a median follow-up for survivors of 60 months, the 5- and 10-year OS rates following HDT were 66% and 55%, respectively. The 5- and 10-year- EFS rates were 60% and 57%, respectively. 116/193 (60%) patients were alive with no evidence of disease at the end of follow-up. Patients who relapsed after initial CA and thus received TLI-based salvage had a significantly better OS and EFS (logrank P=0.05 and 0.006, respectively) compared to CMT patients. No such difference was seen in patients with primary refractory HL. On multivariate analysis, predictors for worse EFS were less than CR to salvage chemotherapy and initial B-symptoms. Factors associated with improved disease-specific survival (DSS) were CR to initial and salvage chemotherapy, use of TLI and no initial B-symptoms. Poor predictors for OS included less than CR to salvage chemotherapy and pruritus at recurrence; initial B-symptoms were borderline significant. *Conclusions.* Only about 50% of patients with originally early-stage HL survive 10 years following HDT salvage after initial treatment failure; that is similar to advanced-stage patients. Complete response to standard-dose salvage chemotherapy and absence of B-symptoms at initial presentation are associated with significantly better outcome.

C088

RELAPSE OF HODGKIN'S LYMPHOMA AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT): IDENTIFICATION OF PROGNOSTIC FACTORS PREDICTING OUTCOME

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Purpose. To evaluate outcome of patients with relapsed Hodgkin's lymphoma (HL) after high-dose chemotherapy followed by autologous stem-cell transplantation (ASCT) and to distinguish different risk groups using identified prognostic factors. *Patients and methods.* We reviewed 462 adult patients registered in the European Group for Blood and Marrow Transplantation (EBMT) database between 1996 and 2005. Tandem ASCT and patients receiving only palliative care after relapse were not included in the study. *Results.* Median time from ASCT to relapse or progression was 7 months (range, 1-78). Treatment following ASCT failure consisted on conventional chemotherapy and/or radiotherapy in 294 patients (64%), second ASCT in 35 (8%), and allogeneic SCT in 133 (29%). After a median follow-up of 49 months, overall survival (OS) was 32% at 5 years. In multivariate analysis, independent risk factors for OS were early relapse, stage IV, bulky disease, poor performance status, and age >50 years at relapse. For patients with no risk factors OS at 5 years was 62% compared with 37% and 12% for those having 1, and >2 factors, respectively. This score was also predictive for outcome in each group of rescue treatment after ASCT failure. *Conclusion.* In the EBMT database, most HL patients with ASCT failure are treated with chemo-radiotherapy and some of them with a second transplantation. Early relapse, stage IV, bulky disease, poor performance status and age >50 at relapse are relevant factors and could be used to guide the choice of treatment and to understand the results of novel therapeutic approaches.

C089

ALLOGENIC STEM CELL TRANSPLANTATION FOR HODGKIN'S DISEASE: A RETROSPECTIVE ANALYSIS OF DATA FROM THE GERMAN STEM CELL TRANSPLANTATION REGISTRY (DRST)

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High dose chemotherapy with autologous stem cell transplantation is the standard of care for relapsed Hodgkin's disease with high remission rates. However a small proportion of these patients relapse and have been offered allogeneic transplantation, in particular when a matched sibling donor was available. However less information is available on results with unrelated donors and on potential factors influencing outcome. We performed a retrospective analysis of all allogenic stem transplants for Hodgkin's disease registered in the DRST and made a survey among the centers of the GCTSG to cross-check and update the information. Kaplan-Meier-analyses and log-rank-tests were used for survival analyses. A total of 245 patients receiving an allograft from a matched related (n=110) or unrelated (n=135) donor between 1995 and 2009. 165 patients (67%) had received a prior autologous transplantation a median of 11.6 months before allografting. Disease status before allotrans-

plant was CR in 13.5%, PR in 25.3%, sensitive relapse in 13.9% and progressive or resistant disease in 33.9% The median age at transplant was 31 yrs with a range of 11 to 64 yrs. The median follow up for surviving patients was 21 months. Median overall survival for all patients was 16.9 months. There was a strong correlation with the time of transplantation: median OS was 7.2 mo for patients transplanted up to 2000, 9.1 mo between 2001 and 2003, 38.5 between 2004 and 2006 and 25.3mo between 2007 and 2009. There was no significant effect on survival for donor type, prior autograft or age (by decades). There was a trend that better response before allograft was associated with better surival with a median of 28 mo for patients in CR vs 8.4 mo for refractory disease, however this was not statistically significant. In summary these data show an improvement of transplantation results over the last years and the importance of tumor control before transplantation.

C090

EXTENDED FOLLOW-UP OF THE SAFETY OF 131I RADIOLABELLED ANTI-CD25 ANTIBODY, BASILIXIMAB, IN PATIENTS WITH CD25-POSITIVE, REFRACTORY HODGKIN LYMPHOMA

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There remains a need to improve therapies for patients with refractory Hodgkin lymphoma (HL). There is a sound rationale for radioimmunotherapy (RIT) in HL which is a radiosensitive tumour known to demonstrate a range of differentially expressed cell surface antigens that can act as potential therapeutic targets. We report on 33 patients (19 M:14 F) with a median age of 33 years (range 24-77 years) treated with a chimeric antibody to the alpha-chain of the IL-2 receptor, conjugated to iodine-131. We previously reported on a smaller cohort of 12 patients in a dose finding study with limited follow-up. The current group had received a median of 4 previous therapies (range 2-10). The majority (21/33) had received an autologous (ASCT) or allogeneic stem cell transplant (alloSCT). The remaining 12 patients were considered unsuitable because of chemoresistance (9/12) or co-morbidities (3/12). The median remission duration following previous therapy was 5 months (range 1-36 months). Grade 3/4 toxicity was predominantly haematological; thrombocytopenia was seen in 46% of patients with the nadir occurring at 37 days (range 15-47). Non-haematological toxicity included grade 3/4 infections in 6 of 33 patients. With extended follow-up, one patient had experienced hypothyroidism requiring supplementation despite pretreatment with potassium iodide. After a median follow-up period of 14.5 months (range 1-110) 22/33 patients are alive; 2 patients are in ongoing CR (1 had an alloSCT and one patient had no other therapy). Median time to disease progression was 70 days (range 40-288). Eleven of 33 patients died at a median of 408 days following CHT-25 therapy (range 70-752); 5/11 patients died of progressive disease, 3 from sepsis and in 3 patients the cause was unknown. RIT enabled high dose therapy in 4/9 patients with chemoresistance who were subsequently considered suitable for high dose therapy with stem cell support. RIT with CHT-25 is safe and applicable therapy for patients with poor-risk, refractory HL and can enable high dose therapy. Further studies are necessary to evaluate the efficacy of basiliximab therapy, the timing of its use in poor-risk patients who relapse early following ASCT and its ability to render patients suitable for alloSCT.

C091

INITIAL RESULTS FROM THE SAPHIRE STUDY: A PHASE II TRIAL WITH THE NOVEL ORAL HISTONE DEACETYLASE (HDAC) INHIBITOR RESMINOSTAT IN RELAPSED OR REFRACTORY HODGKIN'S LYMPHOMA PATIENTS

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Resminostat (4SC-201) is a novel pan-HDAC inhibitor that has shown anti-tumour activity in a broad panel of preclinical models and revealed a very favourable safety and promising efficacy profile in patients with various solid tumour types in an initial Phase I trial. Resminostat is currently under investigation in a number of Phase II clinical trials. The SAPHIRE study evaluates the therapeutic activity of resminostat in relapsed/refractory Hodgkin's Lymphoma (HL) patients after high dose chemotherapy and/or autologous hematopoietic stem cell transplantation. The trial is composed as an open-label, single-arm international trial with a Simon Minimax design. Resminostat is administered orally at a once daily dose of 600 mg in 2-week cycles consisting of 5 consecutive days treatment followed by a 9 day treatment free period. Dose delay and reduction is allowed for management of adverse events. Patients undergo assessment of disease status by computed tomography in combination with positron emission tomography (PET/CT), as recommended by the International Working Group (IWG) criteria for the evaluation of HL. PET/CT scans are conducted after cycle 3 and cycle 6 and thereafter every 4th cycle during an optional follow-up treatment period in which patients may remain on treatment until disease progression or occurrence of intolerance to protocol therapy. The primary endpoint of the study is the estimation of overall objective response rate (OOR), secondary endpoints include time to response (TTR), duration of response (DOR), safety and tolerability and the study of drug regulated biomarkers in this patient cohort. As of June 2010, 19 patients with advanced HL have been enrolled in the 1st Simon stage of the study. Treatment was well tolerated with common related grade 2 -3 AEs being anemia and thrombocytopenia that were well manageable by dose modification or symptomatic treatment. Analysis of PET/CT data through an independent central assessment committee confirmed the achievement of the clinical activity requirements for the advancement of the trial into the 2nd Simon recruitment phase. Updated clinical data of this ongoing study on the efficacy and safety of the HDAC inhibitor resminostat in relapsed/refractory HL patients will be presented at the meeting.

P092

WHAT CAN BE EXPECTED FROM SALVAGE RADIATION THERAPY WHEN AN AUTOLOGOUS STEM CELL TRANSPLANT (ASCT) FAILS TO CONTROL HODGKIN LYMPHOMA?

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Purpose. Hodgkin Lymphoma (HL) patients with relapsed/progressive disease following ASCT have poor prognosis. The efficacy of salvage radiotherapy (RT) was retrospectively analysed. *Methods.* Among 347 pts with recurrent/refractory HL who received ASCT from 1986-2006, 163 had failed ASCT. Of these, 56 received salvage RT and form the basis of this report. The M: F ratio was 1.3:1, and median age 32 yrs. Nodular Sclerosis accounted for 84%. Previous RT was given in 33 pts (59%). Disease involved extranodal tissues in 24 (43%). RT alone was given in 34 pts (61%), and CMT in 22 (39%). Median interval from ASCT to relapse was 0.51 yrs, and from ASCT to salvage RT, 0.8 yrs. All involved sites were radiated in 39 pts (70%) while the rest were radiated at symptomatic sites only. Median RT dose: 35Gy. RT technique was involved field in 36 (64%) and extended fields in the remainder. Survival was calculated from the start of RT. Disease progression within RT volume was regarded as local failure, while progression outside judged as systemic failure. *Results.* The median follow up from RT was 31.3 months (range 0.2-205.5). The ORR to RT was 84% (CR:36%, PR:48%, SD:11%). The median overall survival (OS) was 40.8 months (95% CI, 34.2-56.3) and 5-year OS: 32%. The 2-year PFS was 16%, with 2-year local PFS: 69%,

and 2-year systemic PFS: 17%. Those with progressive disease after ASCT had worse outcome than those who relapsed. Five pts (9%) had long-term disease-free survival at 6.4, 6.8, 7.4, 7.9 and 17.1 years following salvage RT. At last follow up, 36 pts had died (22 with systemic disease, 11 with both systemic & local disease, and 3 died due to other causes). Among 20 alive pts, 9 had systemic disease, 5 had both systemic & local disease, 1 had local progression alone and 5 were disease free. *Conclusion.* Patients who fail ASCT have a poor prognosis with a very high probability of systemic disease progression. In selected cases RT provides a moderately good 2-year local control rate of approximately 70%, and occasionally leads to long-term survival.

P093

POSITIVE PRE-TRANSPLANTATION POSITRON EMISSION TOMOGRAPHY INDICATES POOR PROGNOSIS IN RELAPSED HODGKIN LYMPHOMA PATIENTS

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Objectives. This retrospective study evaluated the secondary clinical risk score at relapse, the prognostic significance of pre-transplantation positron emission tomography (PET) and achievement of complete remission (CR) assessed by computed tomography (CT) after salvage chemotherapy before autologous stem cell transplantation (ASCT) in 76 relapsed/refractory Hodgkin lymphoma (HL) patients. *Patients and methods.* Progression-free survival (PFS) and overall survival (OS) of patients was calculated using Kaplan-Meier method. Differences of survival between subgroups were analysed with log-rank test. *Results.* Median follow-up of patients after ASCT was 23 months. Overall 11 (55%) of 20 PET positive patients and 14 (25%) of 56 PET negative patients relapsed after ASCT. The 2-year PFS in PET negative vs PET positive patients was 72.7±6.3% vs 36.1±11.6%, respectively (P=0.01). The 2-year OS in PET negative vs PET positive patients was 90.3±4.1% vs 61.4±11.6%, respectively (P=0.009). In univariate analysis, the secondary clinical risk score at HL relapse, primary refractory disease or achievement of CR evaluated according to CT scan were not statistically significantly associated with PFS and OS. In the multivariate analysis PET was statistically significant for PFS only in combination with other variables (clinical risk score and CR assessed by CT), P=0.017. The mutivariate analysis of these variables, however, was not significant for OS (P=0.08). *Conclusion.* Positive pre-transplantation PET identified a high-risk subgroup with worse PFS and OS when comapared to PET negative patients. This high-risk subgroup may benefit from further treatment after ASCT.

P094

PREDICTING RESPONSE TO SALVAGE THERAPY IN RELAPSED AND REFRACTORY HODGKIN LYMPHOMA

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We and others have reported that response on functional imaging (FI) following salvage therapy (ST) is one of the strongest predictors of outcome following autologous stem cell transplant (ASCT) for relapsed and refractory (rel/ref) Hodgkin lymphoma (HL) (Jabbour, *et al.* 2007, Moskowitz A, *et al.* 2008, Moskowitz C, *et al.* 2010). We therefore aimed to identify factors predictive of FI normalization following ST in rel/ref HL. Between 9/1994 and 4/2010, 277 patients with rel/ref HL were treated on 1 of 4 consecutive IRB approved studies at MSKCC. Patients were enrolled at the time of relapse or documentation of refractory disease and treated with ICE (ifosfamide, carboplatin, etoposide)-based ST. Functional imaging (with gallium or FDG-PET) was performed before and after ST. Of the 277 patients, 50.5% were males and the median age was 32. There were 94 (34%) patients with bulky nodal masses (≥5 cm), 117 (42%) with primary refractory disease, 111 (40%) were previously radiated of whom 79 (71%) relapsed in previously radiated fields, 133 (48%) had extranodal disease, 64 (23%) had B symptoms, and 192 (69%) relapsed within 1 year of initial treatment. 271 patients underwent evaluation with FI before and after ST; 62% of these patients were evaluated with FDG-PET. 165 (60%) patients achieved normalization of functional imaging following ST. Univariate and multivariate analysis to identify factors associated with failure to normalize FI appear in the table. Four factors remained significant by multivariate analysis: bulk ≥5 cm, relapse within previously radiated fields, relapse within 1 year of initial treatment, and presence of B symptoms at relapse. The numbers of patients with 0, 1, 2, 3, or 4 risk factors were 31, 100, 83, 38, and 4 and the rate of FI normalization by risk factor group was 87%, 76%, 50%, 34%, and 0% respectively. Patients with 2 or more risk factors are at high risk of remaining FDG-avid following salvage therapy and are therefore much less likely to be cured with ASCT. Clinical trials evaluating novel and /or more intensive salvage regimens in this risk group are needed with the primary endpoint of a negative pre-ASCT FDG-PET scan.

Table.

Characteristic	*p-value UVA*	*p-value MVA*	*Hazard ratio (95% CI)*
Age	0.74		
Gender	0.61		
Bulk ≥5 cm (at relapse)	<0.0001	<0.0001	3.12 (1.78-5.47)
Bulk ≥10 cm (at relapse)	<0.006		
Previous RT	0.72		
Relapse in radiated field	0.05	0.008	2.32 (1.24-4.33)
Relapsed vs. Refractory	0.0004		
Relapse within 1 year	0.008	0.010	2.35 (1.23-4.48)
Extranodal disease	0.0003		
B symptoms (at relapse)	<0.0001	0.005	2.53 (1.33-4.80)

P095

LOCAL CONTROL, DISEASE-SPECIFIC, AND OVERALL SURVIVAL IN REFRACTORY OR RECURRENT HODGKIN LYMPHOMA MAY BENEFIT FROM INVOLVED FIELD RADIATION THERAPY THAT FOLLOWS HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANT

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Introduction. Patients with recurrent or primary refractory Hodgkin lymphoma (HL) treated with high dose chemotherapy (HDC) and autologous stem cell transplant (ASCT) commonly relapse post-ASCT in sites of previous disease. Although adjuvant involved field radiation therapy (IFRT) to sites of previous recurrence might be expected to enhance local control, translation of this into improved disease-specific (DSS) or overall (OS) survival is controversial. We sought to evaluate IFRT following ASCT in terms of patterns of recurrence, OS, and DSS. *Methods and materials.* Between May 1993 and October 2003, a total of 62/66 evaluable patients with refractory/recurrent HL underwent HDC followed by ASCT. Thirty-two (52%) patients received IFRT following transplant and thirty (48%) patients did not. Survival was calculated from the day of stem cell infusion. *Results.* The median follow-up was 2.3 years (range 0.03-11.56 years). The estimated 5-year OS and DSS was 63.3% & 82.1% with IFRT, and 40% & 57.6% without IFRT (P=0.07 and P=0.08, respectively). Presence of B-symptoms was adverse on both univariate and multivariate analysis (P=0.007 & P=0.01, respectively). Patients receiving IFRT following transplant were less likely to fail locally (P=0.03). *Conclusion.* Recognizing that positive and negative patient selection bias exists for the use of IFRT post-ASCT, patients with recurrent or refractory HL treated with HDC /ASCT benefited from IFRT in terms of local control . These patients also had a marginal benefit in OS and DSS at 5 years. Given the retrospective nature of our study, a future prospective study is warranted to clarify the value of IFRT in the transplant setting.

P096

ACTIVITY, SAFETY AND TOLERABILITY OF ANTIBODY-DRUG CONJUGATE (ADC) SGN-35 IN RELAPSED/REFRACTORY (R/R) HODGKIN LYMPHOMA (HL) AND CD30+ HEMATOLOGIC MALIGNANCIES

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SGN-35 is an anti-CD30 antibody conjugated to the highly potent antitubulin agent, monomethyl auristatin E (MMAE), by a plasma-stable linker. SGN-35 selectively induces cytotoxicity in CD30+ cells by binding, internalizing, and releasing MMAE. CD30 is present on malignant Hodgkin Reed-Sternberg (RS) cells, anaplastic large cell lymphoma (ALCL) and other T-cell lymphoproliferative disorders, but has limited expression in healthy tissue or resting leukocytes. The first phase I study evaluated SGN-35 q3wk IV infusion in R/R CD30+ malignancies, including 42 HL and 2 ALCL patients, primarily after autologous stem cell transplant (ASCT). Of 28 evaluable patients receiving ≥1.2 mg/kg, 93% had tumor reductions, 54% objective response (ORR) and 39% complete response (CR). SGN-35 was generally well tolerated. The majority of treatment-related adverse events were Grade 1/2; the most common were fatigue, fever, peripheral neuropathy, diarrhea and nausea. (Younes *et al.*, 2009) A second phase I study evaluated weekly dosing of SGN-35, primarily in HL patients relapsing after ASCT. ORR was 56%; CR, 33%. The majority of treatment-related adverse events were Grade 1/2; the most common were peripheral neuropathy, fatigue and nausea. (Fanale *et al.*, 2009). Preliminary data from a re-treatment case series suggested most patients re-treated with SGN-35 after relapse may experience tumor regression. (Bartlett *et al.*, 2010). A phase II pivotal study is evaluating SGN-35 1.8 mg/kg q3wk in R/R HL following ASCT, with data expected in 2010. (ClinicalTrials.gov. NCT00848926) In addition, a phase II study is evaluating SGN-35 1.8 mg/kg q3wk in R/R systemic ALCL, with data expected in 2010. (ClinicalTrials.gov. NCT00866047). The phase III AETHERA trial (ADC Empowered Trial for Hodgkin to Evaluate PRogression after ASCT) will support and build on previous trials and further characterize the clinical profile of SGN-35. This randomized, double-blind, placebo-controlled, multicenter trial is evaluating the potential of SGN-35 to prevent relapse post-ASCT in patients at high risk of residual HL. After ASCT, participants will receive SGN-35 1.8 mg/kg q3wk and best supportive care (BSC) or placebo and BSC for up to approximately 12 months. The primary end point is progression-free survival; secondary end points include overall survival, safety, and tolerability. (ClinicalTrials.gov. NCT01100502).

P097

GEMCITABINE, DEXAMETHASONE, AND CISPLATIN (GDP): EFFECTIVE AND WELL-TOLERATED SALVAGE THERAPY FOR RELAPSED/REFRACTORY HODGKIN LYMPHOMA (HL)

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Introduction. The optimal choice of salvage therapy for patients with relapsed/refractory HL remains unknown, as available regimens have not been directly compared. The combination of gemcitabine 1000 mg/m^2 IV day 1,8; dexamethasone 40 mg PO days 1-4 and cisplatin 75 mg/m^2 IV day 1 (GDP) induces high response rates with low toxicity (Baetz, Ann Oncol, 2003). Since 2002, GDP has been the primary salvage regimen utilized in British Columbia (BC). *Patients and Methods.* We used the BC Cancer Agency Lymphoid Cancer Database to identify all prospective patients with relapsed/refractory HL treated with GDP. *Results.* 82 patients were identified. Clinical characteristics at the time of initial diagnosis: 60% stage III/IV, 35% bulky disease >10 cm, 54% B symptoms; 79% nodular sclerosing, 4% mixed cellularity, 2% lymphocyte-rich, 2% nodular lymphocyte predominant, 13% HL NOS. IPS variables were retrievable on 54 patients: 82% IPS<3, 18% IPS>4. Median age at time of GDP, 41y (range, 17-73). Of the 72 (88%) patients treated with GDP in first relapse/progression following ABVD-like therapy, 26 (36%) had primarily refractory HL. Median time to relapse after first-line ABVD (excluding primary refractory) was 18 months (range, 9-189). Response to GDP was available for 46 patients: 3 (7%) CR, 29 (63%) PR, 6 (13%) SD, 8 (18%) PD. In total, 66 (92%) patients proceeded to HDCT/ASCT. With a median follow-up of 30 months (range, 1-77), 61 (85%) patients were alive and 11 (15%) had died (all HL). 5-y progression-free survival (PFS) and overall survival (OS) were 46% and 76%, respectively. Primary refractory patients had a poorer outcome than those with relapsed disease, 5-y PFS (23% versus 55%, P=.132) and OS (57% versus 82%, P=.197). Hospitalization was uncommon (n=5,7%) and no failures of stem cell mobilization nor toxic deaths were recorded. A minority of patients (n=10) were treated with GDP for 2nd/3rd relapse; response rates in this cohort were 10% CR, 70% PR and 10% PD; 30% proceeded to HDCT/ASCT. 5-y PFS and OS were 36% and 90%, respectively. *Conclusion.* GDP is a very effective well-tolerated outpatient salvage regimen for relapsed/refractory HL with outcomes comparable to those reported with more aggressive regimens.

P098

SUCCESSFUL RITUXIMAB-BENDAMUSTINE TREATMENT IN PROGRESSION OF HODGKIN LYMPHOMA AFTER AUTOLOGOUS HEMATOPOIETIC STEAM CELL TRANSPLANT (AUTO-HSCT)

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Objectives. Treatment of post autologous-HSCT progression or relapse of Hodgkin lymphoma (HL) is not yet clear, allogenic hematopoietic stem cell transplantation (allo-HSCT) can be curable if it is done in complete remission (CR). *Case report.* In March of 2007 nodular sclerosis subtype of classical HL was diagnosed in a 22-year old woman, her clinical stage was II /AX (peripheral bulky) with unfavorable prognosis. In April of 2008 after 3 months in CR followed the 8 course of ABVD and 36 Gy cumulative dose of involved field irradiation disseminated relapse was recognized, which was confirmed by 18FDG-PET/CT. For salvage therapy DHAP was started, but after 2 cycle of chemotherapy progression was noticed in 18FDG PET/CT, so the treatment was modified to IGEV, and two cycle of this led to complete metabolic remission (CMR) confirmed by the PET/CT scan. After the IGEV mobilization successful steam cell collection was done, but shortly we recognized a rapid progression of the lymphoma so a total body irradiation was applied before the R-mini-BEAM conditioning. On the 100 days post transplantation (post-Tx) 18FDG-PET/CT multiplex nodal and extranodal (osseal, pulmonary) progression appeared so ICE rescue treatment was started, which was ineffective. Based on the literature's data rituximab-bendamustine (RB) therapy was started for the treatment of the post-Tx progression of HL. After 4 cycles of RB there was CMR on the PET/CT, so we are planning to make an allo-HSCT with reduced intensity conditioning as the patient has no sibling donor. *Conclusions.* Based on our case the rituximab-bendamustine salvage therapy can be suitable for the treatment of the post-Tx progression or relapse of the HL.

P099

A RANDOMIZED PHASE II STUDY OF BORTEZOMIB PLUS ICE (BICE) VERSUS ICE FOR PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN LYMPHOMA

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Background. Bortezomib induces apoptosis of Hodgkin lymphoma (HL) cells (Zheng, B *et al.* 2004). We previously evaluated bortezomib plus ICE (ifosfamide, carboplatin, etoposide) in relapsed/refractory HL patients. In this phase I trial 13 patients received bortezomib on days 1 and 4 and ICE (Moskowitz, C *et al.* 2001) on day 1-3. BICE was well tolerated and induced a complete remission (CR) of 33% in a negative prognostic factor group (Fanale, M *et al.* 2008). Responders underwent successful apheresis, autologous stem cell transplant (ASCT), and engrafted. As the next step we are conducting a randomized trial to compare BICE versus ICE. *Methods.* Eligibility includes only 1 prior chemotherapy regimen which needs to contain an anthracycline. BICE

patients receive bortezomib at 1.5 mg/m^2 on days 1 and 4 with ICE on days 1-3 and pegfilgrastim on day 5. ICE patients receive treatment on days 1 to 3 and pegfilgrastim on day 4. Cycles are repeated on day 14 if absolute neutrophil count greater than or equal to 1000/mm^3 and platelets greater than or equal to 90,000/mm^3. Patients are assessed for response after 3 cycles. The primary objectives of this Bayesian adaptive randomization phase II trial are to determine response rates and progression-free survival (PFS). *Results.* 12 patients have been enrolled (8 relapsed, 4 primary refractory). Median age 29 (range 19-59). 9 patients have completed have completed 3 cycles of BICE or ICE and were evaluated for response. BICE patients' responses are: 3 partial remissions (PR) and 1 progressive disease (PD). ICE patients' responses are: 1 CR, 1 PR, 3 stable disease (SD). Five patients have undergone ASCT to date. Median day for retreatment is day 25 for BICE and day 22 for ICE. Reversible grade 4 neutropenia and thrombocytopenia occurred in 50% of the BICE and ICE patients treated. Reversible grade 2 elevations of AST or ALT occurred in 33% of BICE patients. Grade 1 peripheral neuropathy occurred in 1 BICE patient. *Conclusion.* Enrollment continues to this phase II randomized trial. Correlative studies of serum levels of tumor necrosis proteins (TNF) and CC thymus and activation-related cytokine (TARC) are planned.

P100

LATE RELAPSES FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) FOR HODGKIN LYMPHOMA (HL) IN THE ABVD THERAPEUTIC ERA

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ASCT is the standard therapy for relapsed and refractory HL. To determine the long-term outcome of ASCT in the modern "ABVD era," and the impact of allogenic transplantation in pts who fail ASCT, we reviewed all pts with HL who were treated with ASCT between 1990 and 2005 at the University of Rochester. Median follow-up is 10 years. 113 pts (44% female; 89% Caucasian) with documented HL were treated with ASCT for relapsed/refractory HL. At ASCT, median age was 34 years (range 19-66). 75% of these pts were treated initially with ABVD or MOPP-ABVD-hybrid therapy.

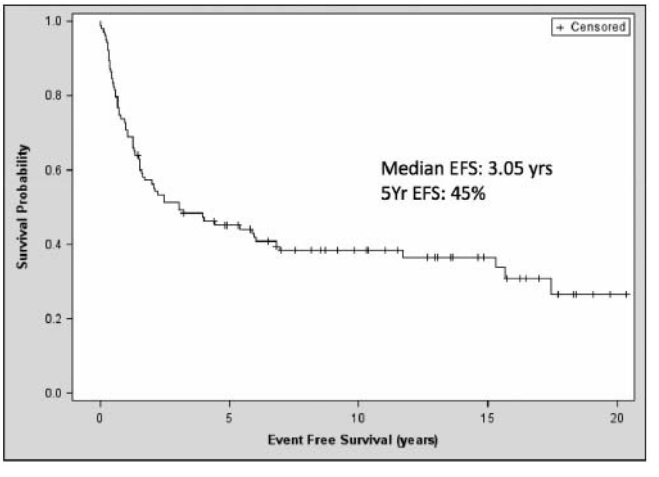

Figure. Kaplan-Meier estimate of event free survival (EFS) for patients receiving ASCT for relapsed Hodgkin lymphoma; University of Rochester, 1990-2005.

Histology was: NS (n=78), mixed cellularity (n=20), LP (n=6), LD (n=3), and classical NOS (n=6). 32% of patients relapsed within 1 year of induction therapy, and 25% were refractory to therapy prior to ASCT. Conditioning regiments at ASCT were BEAC (n=77); BEAM (n=28); Cy/TBI (n=8). 50% of pts received XRT following ASCT. At 5 years, overall survival (OS) for the entire population was 55%, and event-free survival (EFS) was 45%. In total, 67 pts have died; of these 43 died of HL. Notably, 16 (24%) of the deaths occurred more than 5 years after ASCT, and 6 of these 16 patients (38%) died directly from HL; other causes of death were acute leukemia (n=3); 1 each from cardiomyopathy, complications of pulmonary fibrosis, non-Hodgkin Lymphoma, myelodysplastic syndrome, acute myocardial infarction, and 2 unknown causes. Furthermore, 18% of the 56 relapses occurred beyond 3 years, with 6 relapses documented 5 years post ASCT. 14 patients received an allogenic transplant following ASCT relapse: 10 (71%) have died, and only 1 patient remains in remission. In contrast to other studies, we do not observe a plateau in EFS following ASCT. Patients appear to be at continuous risk of recurrence through at least 5 years after ASCT. While it is well-known that there are late events resulting from ASCT, late deaths attributable to HL have not previously been documented. Our results have important implications in defining success of maintenance strategies after ASCT for HL, and emphasize the importance of long-term follow-up for both toxicity and recurrence.

P101

OBJECTIVE RESPONSES WITH SGN-35 RETREATMENT IN CD30-POSITIVE HEMATOLOGIC MALIGNANCIES: A CASE SERIES

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Background. SGN-35 is an anti-CD30 antibody conjugated to the highly potent antitubulin agent, monomethyl auristatin E (MMAE), by a plasma-stable linker. SGN-35 selectively induces apoptosis in CD30$^+$ cells by binding, internalizing, and releasing MMAE. In phase 1 clinical studies, good tolerability and antitumor activity were demonstrated in patients with CD30$^+$ hematologic malignancies. This case series describes patients who have experienced relapse and were retreated with SGN-35. *Methods.* Heavily pretreated, relapsed or refractory patients with CD30$^+$ hematologic malignancies have been retreated with SGN-35 in 3 multicenter studies. Patients had SD with decreasing tumor volume or better (Cheson 2007) with prior SGN-35 treatment, and subsequently experienced relapse. In their retreatment experiences, patients received SGN-35 IV infusions of 1 mg/kg qweek or 1.8 mg/kg q3week, depending on the study. *Results.* Across these 3 studies, 8 patients received retreatment with SGN-35; 3 patients were retreated twice. In the retreatment cases, patients had either systemic ALCL (2) or HL (9) and ages ranged from 16-39 years. At baseline prior to retreatment, ECOG performance statuses were 0/1 (10), or 2 (1). The number of prior systemic therapies (including prior treatment with SGN-35) ranged from 2-11; in 7 retreatment cases, patients had prior autologous stem cell transplant. The most common treatment-related adverse events were peripheral neuropathy, alopecia, arthralgia, and infusion site extravasation; all treatment-related AEs were G1/2 in severity. Responses to retreatment were 2 CR, 5 PR, 3 SD, and 1 PD; tumor regression was observed in all but 1 retreatment patient. All objective responses were observed 5-15 weeks after the start of retreatment, and the range of retreatment response durations is <1 (retreatment ongoing) to 58+ weeks. *Conclusions.* Retreatment with SGN-35 was well tolerated. Objective responses were observed (7 of 11, or 64%) with SGN-35 retreatment in this heavily pretreated population. Enrollment to a phase 2 retreatment study in patients who previously experienced an objective response to SGN-35 is ongoing.

P102

A PHASE II STUDY OF ORAL PANOBINOSTAT IN PATIENTS WITH RELAPSED/REFRACTORY HODGKIN LYMPHOMA AFTER AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANT

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Background. Panobinostat is an oral pan-deacetylase inhibitor (pan-DACi) that increases acetylation of proteins involved in multiple oncogenic pathways. Preclinical studies with panobinostat demonstrated antitumor activity against Hodgkin lymphoma (HL) cell lines at low nanomolar concentrations. Evaluation of panobinostat in the phase I set-

ting showed promising activity in patients with relapsed/refractory HL. *Aims.* This Phase II study sought to determine the efficacy of panobinostat in the post-transplant relapsed/refractory HL population. *Methods.* This study has completed enrollment. Oral panobinostat was administered at a dose of 40 mg three times per week, every week, in 21-day cycles. Dose delay and modification for management of adverse events (AEs) was permitted. Efficacy was evaluated every 2 cycles by CT/MRI scan. The primary endpoint is objective response rate (ORR). Secondary objectives include time to response (TTR), duration of response (DOR), progression-free survival, overall survival, and safety. *Results.* As of April 19, 2010, 129 patients have been enrolled and treated: median age was 32 years (18-75); median number of prior chemotherapeutic regimens was 4 (1-7); median time to relapse after first AHSCT was 8 months (1-198); 80% had 1 or more post-transplant therapies prior to study drug; 37% did not respond (stable disease [SD] or progressive disease) to last prior therapy. Twelve patients also received prior allogeneic transplant. In preliminary efficacy analysis, 129 patients were evaluable for response or discontinued early. A reduction in tumor size was observed in 91 patients (71%) with confirmed responses observed in 33 patients (4 complete responses + 29 partial responses; ORR 26%). As of the data cut-off, median DOR was 7.2+ months. TTR ranged from 4-51 weeks (median 7). Common drug-related Grade 1/2 AEs were diarrhea, nausea, fatigue, vomiting, and anorexia. Common drug-related Grade 3/4 AEs were thrombocytopenia, anemia, and neutropenia. The thrombocytopenia was manageable and reversible with dose hold and modification. *Summary.* This pivotal study represents the largest, prospective, multicenter international trial conducted in this patient population. Interim results demonstrate promising activity of oral panobinostat in post-transplant relapsed/refractory HL patients. Manageable, reversible thrombocytopenia is the most notable AE in these heavily pretreated patients.

P103

HIGH DOSE IFOSFAMIDE AND MITOXANTRONE (HDIM) AS SECOND-LINE CHEMOTHERAPY FOR RELAPSED OR REFRACTORY HODGKIN LYMPHOMA

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Introduction. In this study we examined the toxicity and efficacy of the HDIM regimen for treatment of patients with relapsed or refractory Hodgkin lymphoma (HL) and mobilization of peripheral blood stem cells (PBSC). *Methods.* Between April 2003 and February 2010, 36 patients with relapsed (N=18) or refractory (N=18) HL eligible for autologous stem cell transplantation (ASCT) were treated with two cycles of HDIM (ifosfamide 5 g/m^2 on days 1&2; mitoxantrone 20 mg/m^2 on day 1 and uromitexan 5 g/m^2 on days 1&2 and 2.5 g/m^2 on day 3). PBSC were collected after the first cycle. Median age was 30 years (range 15-47). Patients with (unconfirmed) complete response (CR), partial response (PR) and stable disease (SD) underwent ASCT followed by radiotherapy on regions not in CR prior to ASCT. *Results.* After 2 cycles of HDIM, 15 (42%) patients achieved CR, 8 (22%) PR, 10 (28%) had SD and 3 (8%) progressive disease (PD). PBSC collection was successful in 35 of 36 patients (97%). Subsequently, ASCT was performed in 33 patients. Toxicity was mainly haematological. One patient received only one cycle of HDIM due to nephrotoxicity and another had reversible neurological toxicity. After a median follow up of 22 months, 11 patients had an event (relapse/progression or death of any cause) including four who relapsed after responding to HDIM (CR+PR). Actuarial 2-year event-free survival (EFS) survival was 62%. Overall, seven patients died: three of HL progression, three of allogeneic transplant related complications and one in remission due to pulmonary toxicity after irradiation. Actuarial 2-year overall survival (OS) was 83%. Patients with relapsed disease had better response to HDIM when compared to those with refractory HL (89% vs. 39% for PR+CR, P=0.002) while the difference in 2-year EFS (67% vs. 48%, P=0.12) and 2-year OS (86% vs. 83%, P=0.39) did not reach statistical significance. Patients responding to HDIM had better 2-year OS (91% vs. 69%, P=0.02). *Conclusions.* HDIM is an effective and well tolerated regimen in patients with relapsed or refractory HL. Mobilization of PBSC after HDIM is very successful. Randomized comparisons with other regimens are probably warranted.

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IGEV AN EFFECTIVE SALVAGE AND MOBILIZING REGIMEN IN REFRACTORY OR RELAPSED HODGKIN LYMPHOMA (HL): THE ISTITUTO NAZIONALE TUMORI EXPERIENCE

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High-dose (HD) chemotherapy (CT) supported by peripheral autologous stem cell reinfusion (ASCT) is considered standard therapy for refractory (IF) or relapsed (REL)HL patients (pts).The disease status before HDCT is a relevant prognostic factor; a variety of CT regimens have been used to induce remission prior to transplant, however the optimal regimen is still unknown. Recently the combination of ifosfamide, gemcitabine, vinorelbine and prednisolone (IGEV) has been shown to be effective. The aim of this study was to confirm efficacy and mobilizing potential of IGEV as cytoreductive CT for HL pts eligible for HDCT and ASCT. *Methods.* From October 2006 to July 2009, 21 IF or REL HL pts were given 4 to 6 cycles of IGEV (ifosfamide 2 g/m^2 d 1-4, gemcitabine 800 mg/m2 d 1,4, vinorelbine 20 mg/m^2 d 1, prednisolone 100 mg d1-4), followed by HDBEAM+ ASCT in non progressing pts. *Results.* Main pts characteristics at relapse were: M/F:10/11; median age: 28 yrs; nodular sclerosis/others:16/5; stage I+II/III+IV:12/9; B symptoms: 6; bulky :2; GHSG prognostic index score ≤1/2/3:16/4/1;IF:11, REL:10 (1st CR <12 months:5; 1st CR ≥12 months: 5). The median number of CD34+cells/kg collected after the 1st or 2nd cycle + GCSF was 12.6×10^6 (range 8.3-27.5×10^6). After 2 cycles, PET was negative in 12 (57%) and positive in 9 (43%) pts. Overall response rate was 86% (CR81%); stable disease 5% and progression 9%. Nineteen pts underwent HDBEAM+ASCT. After a median follow-up of 22 months, the 3-year progression-free survival (PFS) and overall survival (OS) were 64% and 95%, respectively. PET-2 results significantly influenced PFS, being 39% vs 82% (P=0.03) in PET-2 positive vs PET-2 negative pts. No significant differences in PFS and OS were observed according to disease status at relapse (REL: PFS 68%, OS 100%; IF: PFS 60%, OS 90%. Treatment was well tolerated and no therapy related death occurred. *Conclusion.* These results confirm that IGEV is a safe, effective and successfully mobilizing regimen and followed by HDBEAM+ASCT may represent an active salvage approach even in refractory pts.

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CURRENT STRATEGIES IN REFRACTORY OR RELAPSED HODGKIN LYMPHOMA

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The German Hodgkin Study Group (GHSG) standard treatment of relapsed or refractory Hodgkin Lymphoma (HL) consists of time-intensified two cycles of DHAP chemotherapy followed by standard BEAM high dose and autologous peripheral stem cell transplant (APBSCT). This dose dense strategy is very effective, but still around 30% of all patients will relapse within the first two years after transplant with the majority of relapses in the first year. Thus, new strategies are needed to further improve the outcome by reducing the relapse rate. In almost all trials in relapsed HL, the disease status before high dose chemotherapy and APBSCT was the most important factor for the prediction of outcome. Because the complete response (CR) rate after DHAP induction is only 21% the GHSG aims to improve the response by adding RAD001 to the induction therapy in the upcoming HDR3induction (HDR3i) trial. RAD001 (everolimus) is a an oral small-molecule inhibitor of mTOR and has demonstrated efficacy in several malignancies. Importantly, it has shown anti-tumor activity in HL cell lines and in relapsed HL patients in a recent clinical trial. RAD001 was well tolerated in all clinical trials, has a distinct mechanism of action from conventional chemotherapy and acted synergistically with cisplatinum in preclinical studies. Therefore, the combination of RAD001 with conventional DHAP induction ("Ever-DHAP") might improve the outcome of relapsed HL patients. Because RAD001 has never been combined with DHAP, this study will begin with a Phase I dose finding trial. Once the maximal tolerable dose of RAD001 in combination with DHAP is defined, the GHSG will conduct a randomized phase II trial of "Ever-DHAP" versus Placebo-DHAP in order to demonstrate efficacy and feasibility of "Ever-DHAP" as induction therapy. Because most patients relapse during the first year after transplant, a maintenance treatment is another reasonable approach which might improve the outcome of relapsed HL patients. The pan-deacetylase-inhibitor panobinostat is a well-tolerated, oral substance

which has shown significant activity in a phase II trial in relapsed HL. Therefore, the GHSG-supported PATH (Panobinostat in Hodgkin Lymphoma) trial which has recently been opened for recruitment will evaluate panobinostat in a placebo-controlled maintenance trial.

P106

THE PROGNOSTIC SIGNIFICANCE OF PET SCAN BEFORE AND AFTER HIGH-DOSE THERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION (HDT/ASCT) IN RELAPSED/REFRACTORY HODGKIN'S LYMPHOMA (HL)

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Objectives. To study the prognostic significance of PET scan before and after HDT/ASCT in relapsed/refractory HL patients. *Methods.* Computed tomography and PET scan were performed prior to ASCT and at 3 months post transplant. PET scan was considered negative when no uptake was present, positive when any lesion was FDG avid with SUV ≥4 and minimal residual uptake positive (MRUp), when any lesion showed abnormal uptake with SUV<4. *Results.* 49 patients were retrospectively studied: 52% were treated for primary refractory disease, 40% at first relapse and 8% beyond first relapse; 76%were chemosensitive prior to ASCT. A PET scan was available in 40 patients prior to ASCT, in 48 post ASCT and in 39 at both time points. Median follow-up was 22.5 months. Pre-ASCT PET scan was positive or MRUp in 18/30 chemosensitive patients vs 10/10 chemoresistant ones. There were 2 relapses among 12 patients with a negative pre-ASCT scan vs 13 among 28 patients with a positive one, resulting in a 1-year FFS of 90% and 51% respectively (P=0.09). The figure of 51% reached a plateau at 8 months post-transplant. Post-ASCT PET scan had a strong predictive value for outcome. One-year FFS was 89% for post ASCT PET negative or MRUp cases vs 14% for positive ones (P<0.0001). Among 39 patients who had a PET scan available at both time points, there were no relapses recorded for those who were pre-ASCT PET scan either positive or MRUp and became post-ASCT PET scan negative (0/13 patients). On the contrary, 12/14 patients with a pre-ASCT PET scan positive or MRUp, who remained or became post-ASCT PET scan positive, relapsed. There were 2 relapses among 12 patients who were pre-ASCT PET scan negative and remained negative after ASCT. There were no cases converted from negative to positive. These differences were highly statistically significant (P<0.0001). *Conclusions.* Pre-ASCT PET scan positivity does not preclude a favorable outcome for patients with relapsed/refractory HL undergoing HDT/ASCT, since half of them remain relapse free. Patients who remain or become PET positive after ASCT have an extremely poor prognosis in contrast to those who convert to negativity.

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IGEV IS A SUPERIOR MOBILIZING AND EQUALLY EFFECTIVE SALVAGE REGIMEN COMPARED TO ESHAP IN RELAPSED OR REFRACTORY HODGKIN LYMPHOMA (HL) PATIENTS

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Background. The standard treatment approach for patients with relapsed or refractory HL is salvage chemotherapy and subsequent high dose therapy and autologous stem cell transplantation (HDT/ASCT). Salvage chemotherapy aims to disease debulking, testing of chemosensitivity, and mobilization of peripheral blood stem cells. Studies comparing different salvage regimens are scarce. Recently the combination of gemcitabine, ifosphamide, vinorelbine and solumedrol (IGEV) has been shown to be an effective salvage and mobilizing regimen in HL. *Aims.* To compare the efficacy of ESHAP (etoposide, methylprednisolone, high dose cytarabine and cis-platinum) vs IGEV chemotherapy as salvage treatment for relapsed or refractory HL patients eligible for HDT/ASCT. *Methods.* Between 2001 and 2006 patients scheduled for ASCT received ESHAP as salvage (n=37), while IGEV was introduced during the last 3 years (n=33). We retrospectively compared these two regimens regarding mobilization, disease control (overall response rate) and a combined endpoint, including both successful mobilization and disease control prior to ASCT. *Results.* Patients' characteristics did not differ between ESHAP and IGEV groups, except of bulky disease at relapse/progression, which was more frequent in the latter (P=0.008). IGEV was more effective as a mobilizing regimen: peak circulating $CD34^+$ cell counts were higher (median 198.6 vs 75.2, P<0.001), the number of total $CD34^+$ collected cells was higher (median 11.6×10^6/kg vs 4.32 $\times10^6$/kg, P<0.001), while all patients were successfully mobilized with IGEV vs 90% with ESHAP. The median time to apheresis was shorter with IGEV (12 vs 16 days, P<0.001), while 21% of patients who underwent stem cell collection with ESHAP vs 5% with IGEV required 2 days of apheresis. Moreover, IGEV was administered as an outpatient regimen. In addition, time to neutrophil engraftment following ASCT was faster with IGEV (median 9 vs 10 days, P=0.002). Overall response rate was similar (50% vs 51% with ESHAP vs IGEV). The combined endpoint of successful mobilization and disease control was achieved in a similar percentage of patients with both regimens (49% vs 55%). *Conclusions.* ESHAP and IGEV have comparable efficacy regarding disease control in relapsed/refractory HL patients as salvage chemotherapies. However, IGEV is a more effective and convenient mobilizing regimen compared to ESHAP.

P108

GALIXIMAB, AN ANTI-CD80 PRIMATIZED MONOCLONAL ANTIBODY, IN RELAPSED HODGKIN LYMPHOMA (HL): FINAL RESULTS OF CALGB 50602

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Background. The average survival of patients with relapsed HL ineligible for transplant or relapsed despite stem cell transplant is approximately six months. Most patients are heavily pretreated and poorly tolerant of additional cytotoxic therapies. CD80 is strongly espressed on the majority of Reed-Sternberg cells, but has limited expression on normal other cells. Galiximab is a primatized IgG1 monoclonal antibody with high affinity binding to CD80 (B7.1), and induces cross-linking of CD80 molecules and death via ADCC. *Methods.* CALGB 50602 is a phase II study of single agent galiximab in relapsed HL after >2 prior regimens. Entry criteria included ANC ≥500/ L and plts ≥50K/ L. Galiximab dose was 500 mg/m^2 weekly × 4 weeks followed by 500 mg/m^2 q 4 weeks until progression or toxicity; overall response rate was the primary endpoint. *Results.* 15 male and 15 female patients with cHL were accrued at 10 CALGB institutions over six-months (6/2008-1/2009). Median age was 36 yrs (range, 22-70) and pts had a median of 3 (range, 1-7) prior regimens. 21 pts (72.4%) had prior RT and 24 pts (82.8%) had failed prior autologous and/or allogeneic stem cell transplant. 1 pt never started treatment. ORR was 10.3% (1CR, 2PR); two responders progressed at 7.5 and 3 months, respectively. 9 patients (31%) had SD. 24 pts came off study treatment for PD. The median TTP was 1.6 months. However, a subset of patients remained on study for over 5 cycles. The six-month PFS and OS is 0.21 (95% CI: 0.08, 0.37) and 0.93 (95% CI: 0.74, 0.98), respectively, with a median survival of 14.2 months. Galiximab was well-tolerated, with grade 3 or 4 non-hematologic toxicities limited to hypophosphatemia (n=3), elevated SGOT/SGPT (n=2), and infection (n=2). *Conclusions.* Galiximab had limited activity (ORR 10.3%) as a single agent in relapsed cHL. However, it was well-tolerated, and although most patients quickly progressed, there is a subset of patients achieving disease stabilization. Secondary analyses of PET response and FcR polymorphisms are underway. The quick accrual of an otherwise rare disease reflects the continued unmet need for targeted and non-cytotoxic therapies in relapsed HL.

P109

AN ANGIOGENESIS AND INFLAMMATION-RELATED GENE EXPRESSION PROFILE PREDICTS RELAPSED AND REFRACTORY DISEASE CLASSIC HODGKIN'S LYMPHOMA (CHL) TREATED WITH ABVD

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Introduction. Despite high cure and long survival rates achieved in cHL during last decades, the incidence of recurrent disease and late treatment-related sequels are not negligible. Traditional prognostic classifications have a limited ability to predict outcomes, and thus there is an urgent need to incorporate novel prognosticators. Both, angiogenesis and inflammatory response has been linked with the biology of cHL. *Methods.* This is a clincopathological study with a case-control design. Cases (Refractory/Relapsed cHL) and controls (5-years free of relapse cHL) were paired by stage, B-symptoms and Bulky disease. 220 cHL patients were consecutively and homogeneously treated (ABVD chemotherapy) in our centres between 1991 and 2005. After histological and immunohistochemical confirmation of cHL, RNA was extracted from formalin-fixed paraffin-embedded biopsies from 30 pairs of matched cases and controls. 96 genes were analysed by duplicate using TaqMan low-density arrays in 22 pairs of cases-controls with preserved 18S. Gene expression levels were normalised using geNorm software. Prognostic factors were derived using multiple regression analysis with SPSSv15.0. *Results.* 44 patients were included, median age was 27 years (range 15-70), male/female ratio was 0.9, performance status was <1 in 84%. Most frequent cHL subtype was nodular sclerosis (61%). Ann-Arbor stage was I in 9%, II in 32%, III in 27% and IV in 32% of patients. 50% presented B-symptoms and 23% had bulky disease. Median follow-up was 87 months (range 1-143). A four genes signature, which included CD9, cathepsin-L1, Endothelin-1 and VEGFR-3, was significant associated with refractory/relapsed cHL with a specificity of 95% and a sensitivity of 91%. In addition, CD9, Lysozime, endothelin-1 and Cox-2 expression and number of nodal areas affected were associated in the Cox Regression with the event-free survival. SerpinH1, VEGF-A, VCAM, VEGF-C and Cox-2 were associated in the multivariate analysis with overall survival. *Discussion.* Current advances allow the study of gene expression profiles from paraffin-embedded tissues. We have identified a four genes signature related to angiogenesis and inflammation which is able to differentiate relapsed/refractory cHL with a high specificity and sensitivity. Confirmatory immunohistochemical studies are undergoing and will be presented.

P110

SECOND MALIGNANCIES AFTER HODGKIN'S LYMPHOMA : THE THIRTY-FIVE YEAR YALE UNIVERSITY EXPERIENCE

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Purpose. Second Malignancies (SMNs) after Hodgkin's Lymphoma (HL) has been a significant cause of morbidity and mortality in survivors that has driven change in treatment protocols. Our institution was an early advocate of low dose involved field radiotherapy (IF-RT) as a part of combined modality therapy (CMT). Chemotherapy in our CMT programs has shifted from initial alkylator based regimens (e.g. MOPP) to doxorubicin-based regimens (e.g. ABVD) while IF-RT has been in the 15 to 30 Gy range, but mostly 21-25 Gy. Since the mid-1990s, early stage adult patients were predominantly managed with CMT as an alternative to prior extended field radiation protocols with doses of ≥40 Gy. This shift to CMT occurred earlier in children. With 35 years experience at Yale spanning these shifting treatments, our study aims to compare the incidence of SMN between high dose RT and CMT with low dose IFRT. *Patients and methods.* Charts and radiation data of 550 patients treated at Yale-New Haven Hospital between 1970 and 2004 for HL were reviewed. The observed number of SMNs was compared to the expected rate of cancers in the U.S. population using Surveillance Epidemiology and End Results data . We compared three groups: RT only (n=275), stage I/II CMT (n=134), and stage III/IV CMT (n=141). We also examined the association with chemotherapy regimen and radiation exposures to specific lymph node regions. *Results.* 42 SMNs occurred among the 550 patients. The risk of a non-hematological SMNs was significantly elevated in the RT only group, with a standardized incidence ratio (SIR) of 1.79 (95% Confidence Interval (CI) =1.15-2.67). Breast and lung cancers were most common, associated with axillary field RT. The 30-year incidence of non-hematological SMNs was 20% with mean follow-up of 15.3 years. For Stage I/II CMT patients, the SIR was 1.13 (95% CI=0.37-2.64) for any SMN and 1.02 (95% CI=0.28-2.62) for non-hematological SMNs. For stage III-IV CMT patients, the SIR was 2.04 (95% CI=1.08-3.48) for any SMN and 1.08 (95% CI=0.39-2.34) for non-hematological SMNs. The 30 year incidence of non-hematological SMNs was 10% and 8% for Stage I-II and Stage III-IV CMT patients, respectively. Among the Stage III-IV CMT patients, there was an SIR of 11.82 (95% CI=4.77-24.43) for hematological SMNs, probably related to MOPP-type chemotherapy. ABVD plus low dose IFRT has a 5% incidence of SMNs at 20 years, considerably lower than MOPP-type regimens. *Conclusion.* More recent treatment strategies for HL utilizing low dose IF-RT and less toxic chemotherapy appear to result in lower incidences of non-hematological SMNs, which overlap the cancer risk in the general population. The incidence of hematological SMNs may also be decreasing. Our findings should be verified in larger cohorts of patients treated with modern HL regimens.

Survivorship

C111

A COMPREHENSIVE PROSPECTIVE NATIONAL DATABASE TO ENHANCE BREAST CANCER (BC) SCREENING SERVICES FOR HODGKIN LYMPHOMA (HL) SURVIVORS TREATED WITH SUPRADIAPHRAGMATIC RADIOTHERAPY (SRT) IN ENGLAND

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In women <35 years with HL, SRT results in an increased risk of BC. Recently we reported the results of a nationwide notification risk assessment and screening programme (NRASP) from the largest English Cancer Network (BJC 2009 p582-88). The increased incidence of BC was confirmed along with some evidence for the efficacy of screening with less frequent axillary lymph node involvement in cancers detected in the NRASP (0/5 vs 7/13; P<0.1). Of concern, only 243 of 417 (58%) women invited attended for clinical review and of the 201 referred for immediate screening results could only be retrieved for 171 (85%). These difficulties led us to propose and commence construction of a comprehensive national database of all women treated with SRT for HL at a young age, populated prospectively at the time of SRT treatment. This comprises: 1. Retrospective Database: BC screening and incidence data from >4000 women consented into the NRASP in 2003/4 have been collected and form the backbone of the database. National Cancer Intelligence Service searches cross-referenced with treating hospital Oncology Management System searches will collate the subsequent 2004-2010 retrospective cohort. 2. Prospective Database: Since April 2009 all SRT delivery is recorded and returned centrally in England as part of the Radiotherapy Dataset (RTDS). RTDS returns contain sufficient data fields to identify all eligible women and will be searched annually to populate the database on a prospective basis, with women informed of database entry and offered the opportunity to opt-out. 3. Robust Breast Screening Programme: Using the national database breast screening appointments will be generated automatically, 8 years after SRT or at age 25 whichever is later. Results of screening in this high risk group will be returned centrally and compared with the general UK screened population to investigate the relative risks of BC over a period when treatment paradigms for treatment of HL have undergone significant change. We describe a national database/screening programme for women at high risk of BC after treatment for HL that intends to overcome the current problems of case identification/recall and facilitate audit of the service and primary research of treatment related BC.

C112

A PROSPECTIVE STUDY OF BREAST MAGNETIC RESONANCE IMAGING (MRI) AND MAMMOGRAPHIC SCREENING IN LONG-TERM FEMALE HODGKIN LYMPHOMA (HL) SURVIVORS

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Women irradiated at a young age for HL are at increased risk for breast cancer. Studies on genetically-predisposed women have shown a significantly higher sensitivity of breast MRI over mammogram in breast-cancer detection. However, data on MRI screening in the HL population is lacking. This study aims to compare the sensitivity and specificity of mammography versus breast MRI for breast-cancer detection in survivors of HL. Between 2005 and 2010, 148 women treated with mantle irradiation for HL at age younger than 35, now more than 8 years beyond treatment, were enrolled. Participants underwent yearly breast MRI and mammograms for 3 years. To date, 135 patients had at least one, 97 had at least two and 60 had all 3 sets of imaging. Fifty biopsies were performed in 38 women based on abnormal imaging (23 MRI alone, 14 mammogram alone and 13 both). Sixteen (32%) showed breast malignancies, including 6 invasive ductal, 9 ductal carcinoma in-situ (DCIS) and 1 phyllodes. One additional case of DCIS, missed by imaging, was found on prophylactic mastectomy of the contralateral breast in a patient. Of the 16 screen-detected breast malignancies, 7 were detected in each of years 1 and 2, and 2 in year 3. The sensitivity of mammogram versus MRI was 0.4 versus 0.6 (P=1.0) in year 1 and 0.3 versus 0.5 (P=1.0) in year 2. The specificity of mammogram versus MRI was 0.98 vs. 0.91 in year 1 and 0.95 vs. 0.96 in year 2. The sensitivity of mammogram and MRI together was 1.0 and 0.88 in years 1 and 2, respectively, and the corresponding specificity was 0.84 and 0.88. The addition of MRI led to the detection of 5 breast malignancies missed by mammogram, but also resulted in 18 biopsies with benign findings in 14 women. This study did not find a significantly higher sensitivity of MRI over mammogram in breast-cancer detection for female HL survivors. MRI as an adjunct to mammogram uncovered additional breast cancers, but at the expense of extra biopsies. Additional data, including cost data, are needed to confirm the role of breast MRI screening in this population.

C113

CORONARY ARTERY DISEASE IN PATIENTS TREATED FOR HODGKIN LYMPHOMA: PRELIMINARY RESULTS USING COMPUTED ANGIOGRAPHY TOMOGRAPHY

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Background. Treatments for hodgkin lymphoma (chemotherapy and notably adriamycin, as well as radiotherapy) increase the risk of coronary artery disease. There are very few data on the incidence and the time period during which coronary artery disease can be detected and treated preventively. *Patients and Methods.* Patients treated in our institution for Hodgkin lymphoma with and without radiation treatments to the mediastinum. All patients underwent a thorough risk assessment (usual risk factors as well as oral hygiene, blood C reactive protein levels and chromosomal telomere length measurements). Computed angiography tomography (CAT) was then performed. *Results.* Two hundred and thirty-nine patients entered the study. The median follow-up was 8 years (range 2-37). One hundred and ninety-three patients (81%) underwent CAT. Chemotherapy including adriamycin was given to all patients. Chest radiotherapy (median radiation dose 40 Gy) was delivered to 82% of the patients. Coronary artery abnormalities were demonstrated in 48 patients (25%) with a median time of 8 years after diagnosis. Coronary artery disease was ostial or affected coronary arteries in 25% and 75% of the cases respectively. The median age of the patients at CAT was 44 years (range 20-81). Major abnormalities (11) were observed in 24% and led to 5 stents and one bypass surgery. One death (25-year old woman) occurred shortly after a stent procedure. The other patients with minor and intermediate coronary disease received a medical treatment. *Conclusion.* There is a high incidence of coronary artery disease in patients treated for Hodgkin lymphoma which occurs within a median time period of 8 years.

P114

PSYCHOMETRIC PROPERTIES OF THE MULTIDIMENSIONAL FATIGUE INVENTORY IN BRAZILIAN HODGKIN LYMPHOMA SURVIVORS

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Cancer-related fatigue is the most common symptom among Hodgkin lymphoma survivors. The aim is to describe the validation steps of the Brazilian Portuguese version of the Multidimensional Fatigue Inventory (MFI). The validation was done in two steps. The questionnaire was first translated from English to Brazilian Portuguese with the forward-backward procedure. The internal consistency, construct validity and convergent validity were then evaluated. The MFI was administered along with a general fatigue question and the informed consent form. Data from five different institutions were collected on 200 Hodgkin lymphoma survivors, with a median follow-up of 7 years from diagnosis. The overall Cronbach alfa for the 20 items was 0.84, and the Cronbach

alfa of each of the five dimensions ranged from 0.59 to 0.81. Item scale correlations of each dimension ranged from 0.32 to 0.72. There was a significant correlation between the MFI and the general fatigue question, with a value of 0.64 for the general fatigue dimension and 0.66 for the physical fatigue dimension. The factor analysis yielded a 5 factor solution that explained 65% of the variance. The first factor corresponded to the original general fatigue and physical fatigue dimensions. The second factor identified the original mental fatigue dimension and the fifth factor identified the original reduced activity dimension. Factors three and four consisted of the questions from the original reduced motivation dimension. The Brazilian MFI showed a satisfactory psychometric performance, and is a valid research tool for measuring cancer related fatigue, allowing different dimensions of fatigue to be assessed. General and physical fatigue were grouped together, as has been previously reported, suggesting that these two dimensions of fatigue are not easily individualised. Also, questions from the original reduced motivation dimension were split in two factors, indicating a lack of conceptual unity and suggesting that these questions should be reappraised in newer versions of the questionnaire.

P115

VALIDATION OF THE BRAZILIAN PORTUGUESE VERSION OF THE MEDICAL OUTCOMES STUDY - SOCIAL SUPPORT SURVEY IN HODGKIN'S LYMPHOMA SURVIVORS

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Several studies in the last three decades have documented the effects of social support on physical and psychological well-being, either in healthy subjects on the onset of a stressful event, or in patients with cancer and other chronic diseases. The aim of this study was to assess the psychometric properties of the Medical Outcomes Study – Social Support Survey (MOS-SSS) in Hodgkin's Lymphoma (HL) survivors. The Brazilian Portuguese version of the MOS-SSS was applied to 200 HL survivors treated in Rio de Janeiro, Brazil. All participants were contacted by telephone, and the questionnaire was self-administered at the treatment center or at home, and sent by traditional or electronic mail. The median age at diagnosis was 29 years (16-77) and the median follow-up was 7 years (3.6-12.7) since diagnosis. Among the 200 individuals, 52% were females, 77% had a good International Prognostic Score (<2 factors), 58% had advanced HL, and 92% had been treated with ABVD chemotherapy. Responses to the 19 social support items were skewed toward positive evaluations (item means of 3.32 to 3.80, in a 0-4 possible range of responses). Pearson correlation coefficients among items varied from 0.22 to 0.79. Corrected Pearson correlation coefficients between items and their dimensions varied from 0.57 to 0.76. The internal consistency was evaluated with Cronbach's alpha, and was 0.95 for the overall scale, ranging from 0.78 to 0.87 for the five subscales. The factor analysis yielded a 3 factor solution that explained 67% of the variance. These 3 functional support subscales measured affection/positive social interaction, emotional/informational aspects, and material aspects. Higher socioeconomic status and larger social network were associated with higher levels of all kinds of social support. Better self-perceived health was associated with higher material support. These psychometric properties were similar to those obtained with the original English version of the MOS-SSS and to the previous validation in Brazilian healthy individuals. This Brazilian Portuguese version is now in use to evaluate social support and its association with long-term disease outcomes and quality of life in Hodgkin's lymphoma survivors.

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THE IMPACT OF SOCIAL NETWORKS AND SOCIAL SUPPORT ON QUALITY OF LIFE IN LONG-TERM HODGKIN'S LYMPHOMA SURVIVORS

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As the number of Hodgkin's Lymphoma (HL) survivors increase, there has been a growing interest in the long-term treatment-related side-effects and their impact on the quality of life (QoL). The aim of this study was to assess the effects of social networks and social support on the QoL in long-term HL survivors in Rio de Janeiro, Brazil. In order to assess QoL and fatigue, the generic Short Form-12 (SF-12) questionnaire, the cancer survivor's questionnaire (QoL-CS) and the Multidimensional Fatigue Inventory (MFI) were used. Social network and social support were evaluated with the Social Support Survey (MOS-SSS). A total of 200 HL survivors, with a median follow-up of 7 years (3.6-12.7) were included. All participants were first contacted by telephone, and the questionnaires were self-administered. The median age at diagnosis was 29 years (16-77); 115 (58%) had advanced HL and 92% were treated with ABVD chemotherapy. A linear logistic regression was performed to verify the impact of social network and social support dimensions on the QoL and fatigue measures, after controlling for age, gender, performance status, stage, radiotherapy use, disease progression, socioeconomic status and the patient's educational level. The affective, emotional and informational support were positively associated with the physical component score. The social network, affective, material and positive interaction support were positively associated with the mental component score. The social network and all social support dimensions, except for the material one, were also associated with QoL-CS scores. Regarding fatigue, it was observed that affective, informational, positive interaction and emotional support had a favorable impact on four of five dimensions of the MFI. In summary, the study indicated that both social network and social support impact the QoL and fatigue scores in Brazilian survivors of Hodgkin's lymphoma. This information may be useful in the follow-up of these individuals, and may inform effective interventions by health professionals and community organizations in order to improve the survivors' quality of life.

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DEVELOPMENT OF A NURSE-LED SURVIVORSHIP CARE STRATEGY FOR LONG-TERM SURVIVORS OF HODGKIN LYMPHOMA

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Background. As the numbers of survivors of Hodgkin Lymphoma (HL) grow it is increasingly important that they normalize their lives and incorporate healthy behaviours into their lifestyles in order to achieve optimal health outcomes. *Objective.* The Late Effects (LE) Clinic at Peter MacCallum Cancer Centre was established in 2000. As of June 2010, 55 male and 48 female survivors of HL attend the clinic. Median age is 41 (19-72), median age at diagnosis is 23 (9months-50yrs), and median years since completion of treatment is 17 (4-41). Eighty-six patients received radiotherapy .Sixteen patients have developed a second malignancy. In order to meet increasing patient need within the LE clinic an innovative model of nurse-led care was developed to enhance HL survivors' awareness of individual risks; the benefits of adopting healthy lifestyle behaviours and to reduce psychosocial distress. *Method.* In the nurse-led consultations information is presented to survivors in an education package directed specifically at their health needs. Information addresses physical activity; healthy eating; smoking status; self examination; sun protection, sexual health, fertility and mental health. Screening for emotional distress is undertaken using the LE supportive care needs screening tool. Each survivor receives an individualized survivorship care plan which is shared with their community physician. *Results.* Data collection is in its infancy and is currently being collected using two validated tools: the General Health Index (GHRI) and the Health Promoting Lifestyle Profile II (HPLP–II). They measure whether receiving a health promoting intervention from a specialist nurse consultant demonstrates an improvement in HL survivors' knowledge of and motivation to adopt health promoting behaviors, an improvement in perceptions of health, a reduction in unmet information needs and a reduction in health worry associated with the knowledge of risk of developing LE. *Conclusion.* This innovative nurse-led model of survivorship follow-up is based on best available evidence and is endorsed by a team of experts in the field. As such, this initiative demonstrates an evolution in thinking about the development of nurse-led follow-up and may offer a useful model for the development of other nurse-led models of cancer survivorship care in the future.

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RISK OF MULTIPLE SUBSEQUENT NEOPLASMS FOLLOWING TREATMENT OF HODGKIN LYMPHOMA

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Background. Patients treated for Hodgkin lymphoma (HL) have an increased risk to develop various secondary malignant neoplasms (SMNs) compared with the general population. Patients who survive their first SMN remain at risk to develop further SMNs. Although subsequent SMNs may cause significant morbidity and mortality, the burden of multiple SMNs has rarely been studied. We assessed risk of subsequent SMNs in a large Dutch cohort comprising 2,657 5-year survivors of HL, <50 years at diagnosis and treated in the Netherlands during 1965-1995. *Methods.* We estimated cumulative incidence (CI) of first and second SMNs with death as competing event. Squamous and basal cell carcinomas of the skin were excluded. A Cox recurrent event analysis was performed using a marginal approach to evaluate factors associated with risk of first and second SMNs (sex, age at diagnosis, radiotherapy, chemotherapy and treatment period). Available treatment data included all HL treatment given prior to the first SMN, including treatment for recurrences. *Results.* After a median follow-up of 18.8 years, 582 (21.9%) patients had developed a SMN. Of patients with a first SMN 228 died within one year. Median follow-up of one-year survivors of a first SMN was 4.0 years and 53 patients developed a second SMN. Female breast and lung cancer accounted for 37.3% (127 and 98, respectively) of all first and for 43.4% (17 and 6, respectively) of all second SMNs. The 15-year CI of second SMNs was 12.3% (95% Confidence Interval 8.8-16.4%). For females and males who received radiotherapy above the diaphragm the 15-year CI was 17.2% and 8.7%, respectively. Risk of a first SMN was increased for females (P<0.001), patients who received radiotherapy (P<0.001) and patients receiving chemotherapy (P=0.017). Risk factors were the same for a second SMNs with the exception of chemotherapy (P=0.008 for interaction). Where chemotherapy was associated with an increased risk of a first SMN (Hazard rate (HR) 1.24, P=0.017), it was associated with a decreased risk of a second SMN (HR 0.61, P=0.079). *Conclusion.* Survivors of a first SMN have a substantial risk to develop a second SMN within 15 years after their first SMN.

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HODGKIN'S LYMPHOMA: AN OUTCOME STUDY BASED ON SINGLE CENTER EXPERIENCE

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Introduction. The treatment of Hodgkin's Lymphoma (HL) is considered one among the greatest success of cancer therapy, with a cure rate of about 80%. Thus, sparing toxicity and quality of life became the main goals; long-term side effects may cause a mortality rate exceeding that from HL after 15 y of follow-up. However, while a large number of clinical trials, based on very selected patients population are available, there are very few data about the long-term outcome in unselected population. We reported here a single center experience collected in the last ten years. *Patients and methods.* Since April 1994 until December 2004 a total of 217 consecutive adult HL pts has been recorded. Clinical characteristics were the following: M/F 111/106, stage I-II 155, stage III-IV 59, undetermined 3, B symptoms were present in 75 pts, not reported in 4. Chemotherapy plus Radiotherapy (CT)were performed in 167, Cht in 35, RT in 9, no therapy in 6. 178 pts were treated with full-dose curative intent ABVD (158), MOPP-ABV (23), Stanford V (5), while 30 pts were approached with less intensive therapy/ palliation, based on RT (9), CHLVPP (12) VBM (3) or no therapy (6). Young relapsing/refractory pts were trasplanted with autologous peripheral stem cell. *Results.* After a median follow-up of 5 y 168/217 (77%) were alive in CR, 149 (69%) after first-line therapy, 43/217 (20%) died, 11/43 in CR for unrelated causes, 6/217 are alive with persistent disease. 30/217 (14%) were 65y or older; among them 20 died, 13/20 for disease progression, 7/20 for unrelated causes, 8/30 are alive in CR. only 12/30 were treated with standard therapy (CT or RT alone), depending from stage and histology. *Conclusions.* Our results confirm brilliant worldwide reported data. Survival in older pts, 14% of the whole population, seems not negatively influence overall results, however showing a worst outcome related to comorbidity and side effects or low tolerance to standard therapy. Older pts account for half mortality rate of the whole population.

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FERTILITY STATUS OF YOUNG PATIENTS WITH HODGKIN'S LYMPHOMA (HL) TREATED WITH CHLVVP/ABVV CHEMOTHERAPY: A RETROSPECTIVE ANALYSIS OF 53 PATIENTS

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Fertility preservation is an important goal in the management of young pts affected by HL. The new modern regimens incorporating etoposide and increasing cumulative dosages of alkylating agents might compromise the reproductive function. To assess the infertility rate after chemotherapy, we retrospectively analyzed 114 clinical records of pts receiving our hybrid chemotherapy regimen, in complete remission for at least 12 months and women younger than 45 yrs at diagnosis. 53 pts (15 male and 38 female) met the above mentioned criteria. Fertility status was defined according WHO criteria regarding available sperm analysis, or paternity for male pts, and according to presence of menses or pregnancy for female pts. Median age at diagnosis was 27 yrs (range 16-44); all pts were treated with ChlVVP/ABVV for 6 cycles + radiotherapy in 28 pts (all supra-diaphragmatic), obtaining CR lasting for a median of 59 months (range 12-141); median follow-up is 64 months (range 16-146). In the male patients group, after a median of 86 months from the end of chemotherapy, 6/15 (40%) patients were azoospermic (with one pt azoospermic before chemotherapy), 4/15 (26%) were oligospermic, while 5/15 (33%) pts had a normal sperm count, shape and motility. 4 pts fathered a child (one the in presence of oligospermia). No patients achieved a pregnancy with thawed semen. In the female patient group, 31/38 pts had regular menses with 6 pregnancies (4 full-term pregnancies, 1 ongoing and 1 induced abortion) after a median of 38 months (range 6-63) after chemotherapy; and 7 (18%) pts developed menopause. Fertility impairment rate was 66% and 18% for male and female pts, respectively. Female sex and age at diagnosis for women (<35yrs) correlated with maintained fertility after chemotherapy (P=0.00007 and P=0.0034 respectively) in a univariate analysis. This data confirms the current notion that modern chemotherapy regimens for HL might be burdened with infertility. Semen cryopreservation is an established method to preserve fertility in males and should be recommended to all pts. For women, the role of hormonal therapies is still under investigation, and other strategies such as oocyte or ovarian tissue preservation should be evaluated.

P121

THE PREDICTIVE ROLE OF 18F-FDG PET IN PAEDIATRIC HD: AN ITALIAN MULTICENTRIC STUDY

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Aim. Our study aimed estimating impact of possible predictive factors on progression-free survival (PFS) in paediatric Hodgkin disease (HD), by giving particular attention to interim and end-treatment evaluation with FDG-PET. *Methods.* For the study a total of 37 consecutive patients affected by HD (mean age 13years; range 2-18) and treated in 9 different Italian Centres (AIEOP-LH2004) were included. All patient had a FDG-PET evaluation at interim (after 2/4 cycles of chemotherapy) and after the end

of treatment. FDG-PET was performed according to standard procedure and thus reported as positive (residual, stable or progressive disease) or negative (no pathological uptake) according to visual and/or semiquantitative analysis. Patients were followed up for a mean period of 30 months (range 8-61) and true outcome was defined as remission (no evidence of lymphoma) or disease (progression, stable or relapse), on the basis of combined criteria including clinical, instrumental and histological data. For the study we considered the following factors: stage (I-II 18pts and III-IV 19pts); B-symptoms (16pts); bulky masses (22pts), FDG-PET result at interim (2/4 cycles) and at end-treatment evaluation. A statistical analysis was performed with respect to PFS for all potential predictive factors, both by using Kaplan-Meier survival curves and Cox proportional-hazards regression. A p value <0.05 was considered significant. *Results.* During follow up relapse was documented in 6 cases (16,2%) with a mean PFS of 25,8 months (range 4-61). In 4 cases out of these 6 patients interim-PET was negative, whereas end-treatment PET resulted positive in 5/6 cases. Response rates for interim-PET showed no significant correlation with patient outcome (P=0,678), while end-treatment PET resulted significantly correlated (P=0,015). The Kaplan-Meier analysis too documented similar results: no significant relation between interim-PET and PFS (P=0,30), while statistically significant for end-treatment PET (P=0,002). All the other factors instead considered for the analysis lacked as predictive factors. The end-treatment PET maintained its predictive value also in the multivariate Cox-regression analysis (P=0,028). *Conclusions.* FDG-PET scan at the end-treatment evaluation directly correlates with patient outcome in paediatric and results the only predictor to PFS.

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DEDICATED OUTPATIENT LATE EFFECT CLINICS FOR HODGKIN LYMPHOMA SURVIVORS: A NEW INITIATIVE IN THE NETHERLANDS

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Introduction. The number of Hodgkin lymphoma (HL) survivors has substantially increased as a result of more effective treatments. However, survival and quality of life are affected by long-term complications of treatments. These long-term complications are diverse and include second cancers, cardiovascular disease and dysfunction of various organs. Currently there is no coherent long-term follow-up policy for HL survivors in the Netherlands. *Project.* In 2009 a collaborative project was initiated involving all Dutch university medical centers and several large non-university clinics. The aim of this project is to reduce the morbidity and mortality due to long-term complications of HL treatment and to improve the quality of life in HL survivors, through the institution of follow-up guidelines for screening and intervention. *Methods.* HL survivors will be identified in all participating hospitals. Treatment data will be collected from HL survivors diagnosed from the 1980's onwards. A nationwide infrastructure will be created consisting of HL late effect outpatient clinics in the participating hospitals. HL survivors with a high to moderate risk for long-term complications will be invited to visit the late effects clinic and counselled or screened for breast cancer, cardiovascular diseases, fertility problems, thyroid and spleen dysfunction and other long-term complications of treatment. For this purpose, experts are currently developing specific follow-up guidelines for primary and secondary prevention of long-term complications. Literature on the magnitude of the risk of long-term complications and the efficacy of screening interventions will constitute the basis, supported by existing (inter)national guidelines addressing long-term complications among childhood cancer survivors. For patients, educational materials have been developed and consist of a website and leaflet. The website will focus on long-term complications following historical and current treatments for HL and opportunities to reduce these complications. Finally, a nationwide uniform registry of late effects will be created based on existing databases, to facilitate patient care and to create an infrastructure for scientific research. *Conclusion.* This initiative will significantly contribute to better patient education and improved care and will also provide more detailed understanding of long-term complications and new opportunities for interventions to prevent long-term complications in HL survivors.

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LOW OCCURRENCE OF PREMATURE OVARIAN FAILURE (POF) IN YOUNG WOMEN WHO RECEIVED HORMONAL PREVENTION OF OVARIAN DAMAGE DURING HODGKIN LYMPHOMA (HL) TREATMENT: PRELIMINARY RESULTS OF A RETROSPECTIVE, MULTICENTER GISL STUDY

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Chemotherapy, radiotherapy and high dose therapy (HDT) followed by haematopoietic stem cell transplantation may cause POF in young women with HL because of the massive depletion of the ovarian follicle reserve. Factors affecting the risk of POF include the age at the time of therapy, the types of drug used and the intensity of treatment. Without any ovarian protection, the expected rate of POF is approximately 10-20%, 70% and 90-100% following the use of alkylating-free regimens (ABVD/ABVD-like), alkylating-containing regimens (MOPP/ABV, COPP/ABVD, BEACOPP) and HDT, respectively. We retrospectively evaluated the incidence of POF in postpuberal women who received or did not receive hormonal co-treatment for preventing ovarian damage during HL treatment.The study includes 154 female survivors to HL, aged 14-40 years (median 25) at diagnosis and treated in 11 GISL institutions from 1978 to 2008. To protect ovarian function, 94 patients received GnRHa monthly, 36 patients received oral contraceptives, while 24 did not receive any ovarian protection, according to local guidelines. Overall, 110 patients received alkylating-free chemotherapy and 44 pts received alkylating-containing regimens as first-line or salvage treatment. Two of the 102 irradiated patients received subdiaphragmatic radiotherapy. Fifteen relapsed/refractory patients received salvage treatment with autologous-SCT in 8 cases and auto/allogeneic-SCT in 2 cases. After a median follow-up of 84 months (range 22-384), 22 patients (14%) developed POF, while 132 patients (86%) restored their ovarian function with hypo/hypermenorrhea in 18 cases (12%). We found that patients who received hormonal co-treatment had a significant low incidence of POF, in comparison with patients who did not receive any type of prevention (10% vs 38%, P=0.004). Age >30 years and salvage treatment strongly correlate with POF (P=0.003 and P=0.001, respectively). Interestingly, among the patients who received hormonal co-treatment, first-line treatment with alkylating drugs did not induce an excess of POF, compared with first-line treatment without alkylating drugs (P=0.1). Moreover, among the 10 patients who received SCT, 3 patients recovered normal menses. In our experience, hormonal co-treatment is able to prevent POF especially in patients treated with a single line of polychemotherapy, irrespective of the use of alkylating drugs.

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THERAPY ASSOCIATED SUBCLINICAL CARDIAC INJURY IN SURVIVORS OF HODGKIN AND NON-HODGKIN LYMPHOMA

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Background. Contributions of modern techniques of mediastinal radiation (mRT) and anthracycline chemotherapy (ACT) to cardiotoxicity in Hodgkin (HL) and non-Hodgkin lymphoma (NHL) survivors remains incompletely defined. Identifying pre-symptomatic toxicity may provide the opportunity to prevent progression. We used radionuclide imaging to

assess the effects of mRT and/or ACT on subclinical cardiotoxicity. *Methods.* One hundred HL and NHL survivors without cardiac symptoms were screened with ECG-gated radionuclide perfusion and ventriculographic scans since 8/91. We reviewed the most recent scan (mean 10.9±.06 yrs, median 8.1 yrs since diagnosis). Treatment groups compared were: ACT (n=10), ACT + mRT (n=35) and mRT (n=55). Thirty-four survivors had multiple gated acquisition (MUGA) scans evaluating left ventricular ejection fraction (LVEF) only, while 66 had ECG-gated single photon emission computed tomography scans, which also evaluated myocardial ischemia, end systolic and end diastolic volume indices (ESVI & EDVI). Since we employed sequential shielding of cardiac structures to minimize the risk of injury, mRT dose was determined to the LV (RTlv), base (RTb), and superior heart (RTsup) in addition to maximum mRT dose (maxd). *Results.* Mean LVEF differed among the treatment groups: ACT=53%, ACT + mRT= 56% and mRT=60% (n= 100, P=.015); lower percentages reflect inferior function . Mean ESVI was 39, 34, 25 respectively (n=66, P=.005), and mean EDVI was 75, 72, 59 (n=66, P=.009); higher indices reflect inferior function. Univariate linear regression individually tested the associations between ACT, RT lv, RT b, RT sup, maxd and the cardiac variables. ACT dose was associated with reduced LVEF (n=100, P=.04), increased ESVI (n=66, P=.002) and increased EDVI (n=66, P=.005). mRT doses showed no correlation with cardiac function. Multivariate analysis of ACT+ mRT patients found a significant association between ACT dose and increased EDVI, ESVI. No associations were observed with myocardial ischemia throughout. *Conclusions.* Radionuclide function variables suggest that lymphoma survivors treated with ACT have greater subclinical abnormalities than those treated with modern mRT alone. The volume indices ESVI and EDVI appear particularly sensitive indicators of subclinical cardiac damage, and may suggest a patient population for interventional maneuvers.

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INCREASED RISK OF COLORECTAL CANCER IN PATIENTS TREATED FOR HODGKIN LYMPHOMA: A LONG-TERM FOLLOW-UP STUDY IN THE NETHERLANDS

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After the introduction of modern radiotherapy (RT) and combination chemotherapy (CT), Hodgkin lymphoma (HL) has become the prototype of a curable malignancy. However, it has been demonstrated that RT and CT increase the risk of various second malignancies, such as breast, lung and stomach cancer. So far few studies examined the risk of colorectal cancer (CRC); available studies included few cases and had incomplete follow-up. Our study aims to quantify CRC risk following HL in a Dutch cohort by age at diagnosis, follow-up duration, treatment and attained age. Over the past decades we identified a large cohort of 2657 5-year HL-survivors, diagnosed before age 50 and treated between 1965 and 1995. Follow-up information was obtained from medical records and general practitioners. Complete information on medical status through 2003 was obtained for 94% of the cohort. Median follow-up was 18.8 years. Preliminary results show that HL-patients have a 3.2-fold (95% confidence interval (CI) 2.2-4.5) increased Standardized Incidence Ratio (SIR) of developing CRC compared to the general population, with an absolute excess risk of 6.3 per 10,000 patients/year. After a median follow-up of 20 years, 33 CRC patients were identified (19 colon, 14 rectum). The highest SIR (6.7, 95% CI 2.9-13.2) was seen for patients treated before age 25. Cumulative incidence was 1.6% (95% CI 1.0-2.5) at 30 years of follow-up. Especially for colon cancer, the SIR increased with longer follow-up duration (9.2, 95% CI 3.4-20.1 in 30-year survivors). No increased SIR was found for CRC in patients treated with RT alone. However, a significantly increased SIR was found for patients treated with RT and CT. The SIR was highest (5.6, 95% CI 2.9-9.8) in patients treated with CT and RT below the diaphragm. Results also show that a 40-year old HL-survivor treated before age 25 has the same CRC risk as a 55-60-year old person from the general population. The results, with updated follow-up including more detailed analyses concerning treatment-effects, will be available by fall 2010. *Conclusion.* After more than 15 years HL-survivors have an increased risk of developing CRC, especially when treated with chemotherapy and radiotherapy below the diaphragm.

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RECOVERY OF SPERMATOGENESIS (SP) IN TREATED HODGKIN'S LYMPHOMA YOUNG MALES (HL)

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Background. Recovery of Sp remains the big problem until now. Aim of our study was to assess testicular function in HL survivors. We measured plasma sex steroid hormone concentrations (LH, FSH, Testosterone(T)), analyzed semen quality and achieving fatherhood with and without assisted reproductive technologies (ART). Sperm samples of all patients were cryopreserved before treatment. *Patients and methods.* From 1993 to 2009 66 pts aged 14 to 30 (median 22) yrs were examined: HL IIA-IVB st.- nodal sclerosis 60%, mixed cell type 29%, lymphoid predominance 5%, lymphoid depletion 6%. Mean time of completion of treatment prior to the survey: MOPP/ABVD 13 yrs (9-17); BEACOPP14 1,7 yrs (1-3); BEACOPP esc 6,2 yrs (1-12); ABVD 5,9 yrs (1-10); other types of chemotherapy 7,5 years (range 1-16). Median time of Sp recovering from completion of treatment was: MOPP/ABVD 3-5 yrs; ABVD 2-6 mos; BEACOPP14- 2-12 mos. *Results.* Recovery of Sp after treatment was observed: 6 MOPP/ABVD-60.0% (9 of 15); 6-8 BEACOPP14- 56% (10 of 18); 6-8BEACOPP Esc- 3 of 6; 4-8 cycles ABVD- 9 of 9 and 56% (10 of 18) after different schemes of chemotherapy (ABVD/BEACOPP2,BEACOPP2/ABVD,CHOPP/ABVD,COPP/ABVD, Stanford V). In most cases changes in the levels of sex hormones were noted in 41 % (27 of 66). Increase FSH or decrease LH, T, was observed in azoospermic pts. 8 healthy children were born after chemotherapy; 4 with ART and 14 without it. Azoospermia was observed in 38% (25 of 66) treated pts. *Conclusion.* We make accent on the importance of sperm cryopreservation for all young males before any programs of chemotherapy in HL.

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LONG TERM TOXICITIES IN HODGKIN LYMPHOMA SURVIVORS: A SINGLE CENTER EXPERIENCE OF 35 YEARS

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Introduction. Survival of patients treated for Hodgkin lymphoma (HL) had dramatically improved but is associated with emergence of long term toxicities. The purpose of this study was to assess incidence and risk factors of these toxicities in a single center over the last 35 years. *Methods.* We retrospectively analysed long term incidence of secondary malignancies, pulmonary, cardiovascular, and infectious toxicities in 304 HL patients of 15 to 60 year-old, treated between 1973 and 2007. *Results.* With a median follow-up of 8 years, 68 patients died: 36.6% with progressive disease, 41.5% of treatment-related toxicity (17.6% secondary cancers, 16.2% pneumopathies or other infections, 2.9% cardiopathies, 5.8% other toxicities) and 20.6% of other causes. 51.9% of patients had pulmonary toxicities with frequent chronic evolution and asymptomatic radiological mediastinal or lung fibrosis. Mediastinal radiotherapy and MOPP regimen were both associated with lung toxicity but there is no evidence for a cumulative effect of bleomycin. Cardiac toxicity occurs in 17.1% of patients and increased with ABVD use. The rate of secondary malignancies was 15.1% (including 10.5% of solid tumors and/or 5.3% of haematological malignancies). Solid cancers appear later than haematological malignancies and their incidence increased constantly over time. The most frequent tumors were breast (5.1% among women), skin (2%), or lung (1%) cancers and sarcoma (2%). Haemopathy increased mainly after MOPP chemotherapy. More than 2/3 of solid tumors developed within prior radiation field. *Discussion.* In our series, mortality related to long term toxicity is similar to progressive disease mortality but still increased more than 20 years after initial diagnosis. Asymptomatic pulmonary toxicities are particularly frequent and warrant careful follow-up to detect serious complications. Most of cardiac toxicities appear related to ABVD, indicating than this complication may

increase of in the next decade. We observed an unexpectedly high rate of sarcoma, without any clear explanation. *Conclusion.* Our study underscores high rates of long term toxicity related to HL treatment. Toxic profiles are variables, and mirror therapeutic changes occurred during the past decades. Regarding the constant increase of treatment-related mortality without any evidence for a plateau, a long follow-up of HL patients is highly recommended.

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HODGKIN LYMPHOMA: A UK SCREENING STUDY FOR TREATMENT INDUCED LUNG CANCER HOLYSTIC (PILOT PHASE)

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Most patients with Hodgkin Lymphoma (HL) are cured by modern therapy, but survival is undermined by an increased risk of treatment-related second cancers. A UK national screening programme for treatment-related breast cancer was launched in 2003 but no such scheme exists for men/women at high risk of lung cancer (LC) where the prognosis for disease detected at onset of symptoms is extremely poor. With a long median latency there is however considerable scope for early detection. Crucially, since HL survivors are unlikely to be captured in the UK Lung Cancer Screening Trial (UKLS), screening must be studied separately in HL survivors using tools appropriate for this population. A three-year UK multi-centre pilot proposal has been submitted to the National Awareness and Early Diagnosis Initiative to seek information on patient awareness of LC risk after HL treatment, the importance of quitting smoking, and to investigate the acceptability, feasibility, efficacy and health economic impact of screening for resectable LC in this population. Following completion of a detailed demographic, treatment and smoking history questionnaire, study participants will screened at entry and at 12 months using low dose CT (for peripheral airways LC) and bronchoscopy (for central airway LC). A proliferation biomarker, FLT-PET imaging, will be explored for its potential to improve the management of suspected LC and in particular guide the need for excision of single pulmonary nodules. Using a risk model incorporating the highest risk factors (male/female, smokers at/since diagnosis of HL, treated 5+ years previously at age 40+ with thoracic radiotherapy, alkylating agent chemotherapy alone or any chemotherapy plus thoracic radiotherapy) this study expects to detect sufficient cancers (25+ from 500 screened) to meet its objectives. A multidisciplinary team of oncologists, radiologists, histopathologists, nuclear medicine, and respiratory physicians will centrally review locally reported positive screening results using algorithms adapted from the UKLS and LungSearch Trials to define uniform management (rescreen in 12 months, interval reassessment or immediate referral for LC management) across participating Centres. If this pilot is successful a larger study featuring an optimally designed screening/education programme linked to individualised follow-up plans for HL survivors will be undertaken.

P129

THE TREATMENT OF CHILDREN WITH HODGKIN'S DISEASE (HD) AND PRIMARY IMMUNE DISORDER (PID)

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Treatment results of children with HD and PID confirm high risk rezidive, opportunistic infections, EBV, CMV infections, during treatment. Five children with HD and PID were treated in our hospital with chemo and radiotherapy, two of them receved allogeneic stem cell transplantation (allo SCT). The mean age of these children was 11,6 (from 5 to 14 years old) – one boy and four girls. The diagnosis of primary immune disorder was: Wiskott-Aldrich syndrome (WAS) - one patient, ataxia teangiectasia (AT) – one patient, common variable immunodeficiency (CVI) – two patients, autoimmune lymphoproliferative syndrome (ALS) – one patient. Hodgkins disease was diagnosed in all patients. Between gistology variants (WHO classification) private mixed cellularity subtype (MCS – 4, NS II type - 1). Clinical manifestations represented advanced stage disease (IIIB – 2, IVB -3) and involved skin, extranodal sites (liver -1, bone marrow -1) and B symptoms. The patients were treated by using of the protocol DAL HD 90. Three children receved chemoradiotherapy by DAL HD 90. One patient died during chemotherapy. One patient with AT and HD received only chemotherapy. Four patients had first complet/partil remission (2/2). Two patients had relaps HD (1 early and 1 late). One of them with ALS had early recurrence HD 2 months after the end of treatment. This patient receved salvadge therapy with anti CD20 monoclonal antitela (rituximab 375mg/m 6) and ayto SCT. After ayto SCT he has been having pancytopenia for 16 months (his has received NC=8 108 D 34±5 10^6 /kg) and received allo SCT. However, he died on +120 day after allo SCT, because of the development of EBV infections – B-LPS. One patient had relaps after 2 years in the end of treatment without radiotherapy. One patient died during the first remission HD after allo SCT with reduction conduction. During treatment all patiens had many infections: EBV, CMV menyngoencephalitis, candidemia (Candida guilliermondii), aspergillus, sepsis. Only one patient remained alive and has been having first complete remission HD during 4,5 years. Kaplan-Meier analysis shows overall survival (OS) patients with HD and PID 25+0,04.

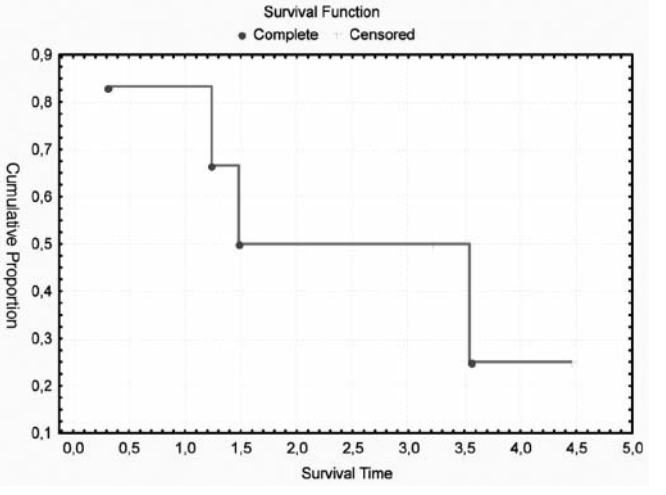

Figure. Overall survival (OS) patients with HD and PID 25±0,04.

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CHARACTERISTIC FEATURES AND TREATMENT OUTCOME OF HODGKIN'S LYMPHOMA AMONG EGYPTIAN POPULATION: A SINGLE INSTITUTION EXPERIENCE

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Background. Hodgkin's lymphoma(HL)is a relatively uncommon malignancy that predominantly affects young adults.It became the first human cancer to be cured with combination chemotherapy. Characteristics & treatment outcome of HL in the Middle East and Africa are not well described. *Patients And Methods.* We conducted a single-institution retrospective review of patients with HL registered at Cairo Oncology Center database over 10-years period (1999-2008). *Results.* One Hundred fifty two patients were identified with confirmed pathological diagnosis of HL. They represented 2% of the total number of patients presented at our center during study period with a male to female ratio 1.3:1. During the same period,the relative frequency of NHL was 7%. The median age of the whole group was 27 years. A Bimodal distribution of age among our patients was detected;with 1st peak in the 3rd decade and second smaller peak in 7th decade. Ninety seven percent of patients were of classical type while Nodular Lymphocytic predominant HL represented 3%. NLPHL was found to have a lower median age (17 years)compared to median age for classic HL (28 years). Among classic HL,CD15 was positive in 95% of cases and CD30 was positive in 97%. Nodular sclerosis had the highest incidence among classic HL representing (56.3%) followed by mixed celluarity subtype(26.4%). Lymphocytic rich subtype and lymphocytic depletion subtypes had lowest

incidence. Seventy percent of patients presented by peripheral nodal involvement (Single sites 16.5% and multiple sites 83.5%). Additional 10% of cases presented with symptoms related to bulky mediastinal disease. The remaining 20% presented by severe B symptoms. Overall,presence of B symptoms was reported in 44.8% of patients. Two thirds of cases (99 patients) presented with early stage(stage I: 28,stage II:71 cases). Among stage IV patients (24 cases). Bone marrow was involved in 10 cases, liver in 8, bone in 4 and lung in 1 case. The vast majority of patients were treated using ABVD regimen as first line treatment.The overall response to first line treatment was 92.5% (77% achieved complete remission while 15.4% achieved partial remission). At median follow-up period of 51 months, 20% of the CR cases had relapsed. The actuarial 5 years survival has exceeded 85% for the whole patient population.Different factors affecting response and survival will be presented during the meeting.

Miscellaneous

C131

FEASIBILITY AND EFFICACY OF ABVD IN ELDERLY HODGKIN LYMPHOMA PATIENTS: ANALYSIS OF TWO RANDOMIZED PROSPECTIVE MULTICENTER TRIALS OF THE GERMAN HODGKIN STUDY GROUP (HD10 AND HD11)

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About 20% of all patients with first diagnosis of Hodgkin Lymphoma (HL) are older than 60 years. They have a poor prognosis mainly due to an increased toxicity of chemo- and radiotherapy. Although resulting in better disease control, aggressive regimens as BEACOPP cuse treatment related mortality of up to 20% in elderly patients. Therefore, ABVD is considered treatment of choice for elderly HL patients, although prospective studies are lacking. We therefore analyzed feasibility and outcome of patients older than 60 years with early favorable- or early unfavorable-stage HL treated with 4 cycles ABVD within the HD10 and HD11 trials of the GHSG. 68 and 49 elderly patients with a median age of 65 and 64 years were treated in HD10 and HD11, respectively. 18% in HD10 but only 8% in HD11 terminated therapy earlier than scheduled resulting in a lower relative total chemotherapy dose (RCD) in HD10. The relative dose intensity (RCD divided by total relative CT duration) was much lower in both studies compared to younger patients, due to more toxicity-related therapy delays and dose reductions, as 4 cycles ABVD caused WHO grade III/IV toxicities in 67% (HD10) and 69% (HD11). Overall efficacy was significantly lower than in younger patients with ORR of 90% in HD10 and 92% in HD11. The rate of relapsing patients was the same as in younger patients in HD11 (14%), whereas in HD10 it was much higher in the elderly (12%) which was mainly due to late relapses. Overall 22% and 37% of the patients died in HD10 and HD11, respectively (median observation time: 92 months). Besides other causes as cardiovascular disease (7%) or secondary neoplasia (5%), there was a high rate of deaths due to insufficient HL-control (5%) and treatment-related toxicities (5%). The five-year PFS estimates for elderly patients were 79% (CI 67% to 87%) in HD10 and 69% (CI 54% to 80%) in HD11 compared to 96% (CI 93% to 97%) and 86% (CI 83% to 88%) for younger patients in HD 10 and HD11, respectively. In conclusion, four cycles ABVD are effective in elderly HL patients however, treatment-related toxicity is high.

C132

A BONE MARROW BIOPSY IS NOT NECESSARY IN THE STAGING OF HODGKIN LYMPHOMA (HL) PATIENTS IN THE FDG-PET ERA

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Accurate staging of patients with HL is essential for tailoring therapy. Traditionally, this has included bone marrow biopsy (BMB). Current guidelines recommend a baseline, pre-treatment FDG-PET in all patients with HL. The utility of functional imaging in detecting bony disease makes the role of BMB unclear and this is reflected in diverse clinical practice in this area. *Methods.* In addition to assessing current UK practice in HL staging by questionnaire we retrospectively analysed patients staged at a single centre with both BMB and FDG-PET to determine the correlation between these two modalities and how disease stage was affected. We also analysed whether clinical parameters predict for marrow infiltration by HL. *Results.* We received 34 responses from 23 centres; 50% of responders used FDG-PET routinely. BMB was employed in 97% with advanced-stage HL. In limited-stage disease a BMB is used in 30% of patients overall, but in 70% of the sub-group of limited-stage HL patients not receiving FDG-PET. Cited indications for BMB in limited-stage disease included an abnormal blood count, sub-diaphragmatic disease & bony symptoms. Six centres provided responses from more than one specialist, but only one of these pairs returned identical answers.There were 50 patients (28 M:22F) with a median age of 38 years (range 18-80); 26% of patients presented with relapsed HL. Ten patients had HL involvement on BMB biopsies (BMB+) all of which were

identified by FDG-PET. Eight cases had bony FDG-PET uptake in the presence of a normal BM biopsy. The majority (5/8) of the BMB-/PET+ cases already had stage IV disease on the basis of CT and FDG-PET imaging findings. There were no patients BMB+ who were FDG-PET-. Clinical and laboratory parameters frequently associated with bony disease included B symptoms (P=0.001), an elevated Hasenclever score (P=0.0027), anaemia (P=0.0069) and HIV disease (P=0.043). *Conclusion.* FDG-PET is more sensitive than BMB in detecting bony involvement by HL. A BMB is unnecessary in patients without bony involvement on FDG-PET prior to treatment. We predict a reduced role for BMB, which should be targeted to FDG-PET+ lesions when clinical stage and therapy would be altered by the result.

P133

SOCIOECONOMIC INEQUALITY AND LONG-TERM OUTCOME IN HODGKIN'S LYMPHOMA

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Socioeconomic status (SES) is a determinant of outcome in various types of cancer. We have previously reported that, with a median follow-up of 1.7 years (0.07-4.35), Hodgkin's lymphoma (HL) patients with a lower SES had a lower survival, with most deaths occurring during ABVD chemotherapy (Int J Cancer 2007;120:875-9). Here we update the follow-up of this cohort, now with a median follow-up of 5 years (0.07-7.24). From 2001 to 2009, 194 consecutive patients were prospectively followed in 5 institutions in Rio de Janeiro, Brazil. Patients answered a questionnaire with a set of items used to determine the SES, and were then divided in 2 groups according to their SES score. There were 151 patients with a higher SES (78%) and 43 patients (22%) with a lower SES. Patients with a higher SES had a higher CR rate than those with a lower SES (85 vs. 72%, crude odds ratio =2.27, P=0.046). A lower SES and a performance status >1 were independently associated with a trend towards a lower CR, even when controlled for the other covariables of interest. Ten patients (5%) died during treatment. Death during treatment was associated with a lower SES (16 vs. 2%, P<0.001), a performance status >1 (P<0.0001), a lower lymphocyte count (P=0.012) and weakly with a lower albumin level (P=0.065). With a median follow-up of 5 years, a higher SES was associated with a better 5-year overall survival (90 vs. 79%, P=0.02) and with a better 5-year progression-free survival (76 vs. 63, P=0.049). Survival differences between higher and lower SES groups were maintained in the 5-year analysis; however, the differences were mainly due to deaths that occurred during the treatment period. In underprivileged countries, patients with a lower SES in chemotherapy could benefit from a detailed explanation of infectious risks and their manifestations, and closer clinical monitoring during treatment. Also, they might benefit from specific medical support measures and a facilitated access to the hospital in case of need.

P134

CLASSICAL HODGKIN LYMPHOMA: THE CLINICOPATHOLOGICAL FEATURES OF NODULAR SCLEROSIS OF THE ELDERLY

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Background. Classical Hodgkin lymphoma (CHL) is characterized by Hodgkin and Reed Sternberg cells in the background with inflammatory cells, and divided into 4 histological subgroups. Nodular sclerosis (NS) is characterized by the mediastinal mass of young adults and good prognosis. However the clinicopathological feature of NS in the elderly (NS-e) remains uncertain. *Patients and methods.* 743 CHL cases between 1986 and 2006 in the Hodgkin lymphoma's multicenter study group were enrolled in the study. To characterize NS-e, we document the clinicopathologic profiles of 84 patients with NS-e (>50 years old), in comparison with 240 NS cases aged 49 or younger (NS-y). *Result.* The cases included 496 men and 247 women, with a median age of 48 years. The diagnoses were NS in 324 cases (43%) and mixed cellularity (MC) in 303 cases (41%). NS cases showed a bimodal age distribution with an initial peak in their 20s and a second small peak in their 60s. NS-e cases numbered 84 and are characterized by male predominance and higher advanced clinical stage (58%) than NS-y. Immunophenotypically, NS-e showed the higher rate for CD20 (24%, 8%) and EBER in situ (39%, 7%) than NS-y. The survival rate of NS-e was poorer than that of NS-y (P<.001) and similar to MC. *Discussion.* NS-e has different clinicopathological features from NS-y, which is considered typical NS. Several NS-e cases might be associated with MC, most of which are EBV-positive. The results suggest the limitation of current histological subgrouping for CHL.

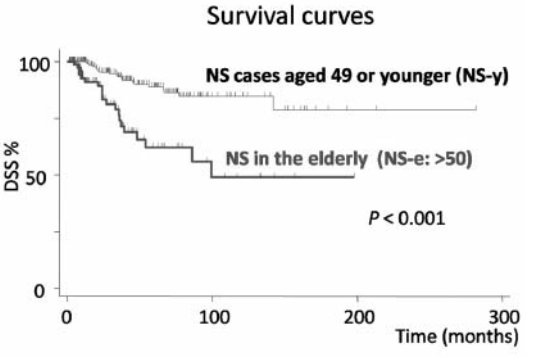

Figure.

P135

THE CLINICAL VALUE OF PET WITH 18F-FDG IN HODGKIN S LYMPHOMA (HL)

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Methods. Forty patients with Hodgkin s Lymphoma at II-IV stages of the disease followed-up using positron emission tomography (PET) in 2006-2009 at our centre. *Results.* One patient has no PET-positive lesions at primary clinical staging in spite of clinical symptoms of the disease. Five patients had lesions proved by clinical and X-ray data, but some regions (cervical and supraclavicular lymph nodes, para-aortic lymph nodes, bones) were negative on PET. In 3 cases specific lesions were proved by PET only. In one case stage of the disease was changed from IIA to IIIA according to PET data (iliac and retroperitoneal lymph nodes involvement which was not detected by other diagnostic methods). All 40 patients had PET after chemotherapy was completed. PET was negative in 29 cases. Only 6 of these 29 patients showed normal size of mediastinal lymph nodes (measured using CT), other 23 patients had enlarged mediastinal lymph nodes. In 26 patients PET was performed after completing chemoradiotherapy. According to PET data, a complete metabolic response was shown by 18 patients, in 5 cases – incomplete response, stabilization of the disease – in 2 patients, progress of the disease in 1 case. This completely coincided with clinical data and other diagnostic methods. After chemoradiotherapy in 29 patients out of 40 a complete clinical remission was shown, in 8 patients – a partial remission, in 2 patients – stabilization of the disease and 1 patient – had progress of the disease. In 4 cases of 40 (10%) relapse was proved by PET at various times after completed treatment. *Conclusion.* PET is an important, but auxiliary component of the patients staging. PET has a great importance at monitoring of the disease course and verification of relapses.

P136

QUALITY OF LIFE OF LONG TERM SURVIVORS WITH HODGKIN'S LYMPHOMA AFTER HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL TRANSPLANTATION AND CONVENTIONAL CHEMOTHERAPY.

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Introduction. High-dose chemotherapy (HDCT) followed by peripheral blood stem cell transplantation (PBSCT) is frequently applied in patients with relapsed or refractory Hodgkin's disease. The toxicity of HDCT, however, might result in a reduced quality of life (QoL). We investigated the QoL of long term survivors after HDCT in comparison with patients after conventional chemotherapy and the healthy German population. *Patients/Methods.* QoL was evaluated with the EORTC QLQ-C30 and the EQ-5D. 98 patients were included in the study: 37 (13 female, 24 male) with a median age of 46 received HDCT with autologous PBSCT between 1986 and 2007. 61 patients (36 female, 25 male; median age 41) were treated with conventional chemotherapy and supplementary radiation. In the conventional chemotherapy group BEACOPP was used in most cases, followed by ABVD, a combination of both or ABV. All patients were in continuous clinical remission. Median follow-up is 11 years (HDCT group) versus 3.5 years (conventional chemotherapy group). In addition, Qol of the patients was compared to QoL of healthy people on the basis of two studies about the general health status of the German population. *Results.* Both groups show a reduced QoL compared to the reference population. The one sample t-test reveals a significant decrease in QoL with $P<0.05$ in several subcategories of the functional state and the symptomatic state. Compared to the conventional chemotherapy group, there is a tendency towards reduced QoL in patients with HDCT in the three main categories of the EORTC-QLQ-C30. However, these differences were not statistically significant, with the exception of the subcategory of dyspnoea. In the EQ-5D, there was a trend for reduced QoL of HDCT patients, however these effects were not significant. *Conclusions.* Since QoL is reduced in both groups compared to the German reference population, we conclude that the negative impact of both HDCT and conventional chemotherapy on the QoL of long term survivors with Hodgkin's Lymphoma should not be underestimated and less toxic therapy strategies should be developed.

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PREGNANCY AND CHILDBIRTH IN HODGKIN'S LYMPHOMA PATIENTS AFTER TREATMENT WITH RADIOTHERAPY AND CHEMO-RADIOTHERAPY

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Introduction. Advances in therapy for Hodgkin's lymphoma (HL) have led to growing numbers of survivors, and late effects of the therapy have become critical, the fertility being one of them. *Methods.* The record of 277 female patients treated for HL (age 15-31, median 21)from 1967 to 2008 at the MRRC, Russia, were analyzed for pregnancy course and childbirth. There were 73,7% of women with HL Stage I-II; 13,9% - Stage III; 12,4% - Stage IV. Treatment programs: supradiaphragmatic and splenic irradiation in total tumor doses (TTD) 40Gy (n=73); 1-6 cycles COPP followed by supradiaphragmatic, splenic (n=167) and paraaortic (n=11) irradiation in TTD 40Gy; chemotherapy COPP alone (n=6); 6-8 cycles COPP (n=5), COPP/ABV (n=2), ABVD (n=7), BEACOPP (n=6) and irradiation of involved sites in TTD 20-30Gy. Radiotherapy was extended to extranodal sites in 28 patients. *Results.* Between 1971 and 2009 a series of 277 women (age 19-37, median 25) gave birth to 335 children. One episode of childbirth had 224 women, two - 44, three - 4 women, and 1 woman had 4 episodes. Three women gave birth to twins. 52,1% of women became pregnant in 1-3 years, 21,7% - in 4-5 years, 26,2% - in 6-17 years after treatment. Most women had normal pregnancy course. Miscarriage occured in 6 women followed by next pregnancy and normal childbirth. There were 11 episodes of premature birth. Three women had operative delivery. Most of the children were born healthy. Eight children (2,38%) had congenital pathology: heart disease (n=2), microcephaly (n=2), sensory hypoacusis (n=2), a cleft lip (n=1), muscle hypotrophy (n=1). Two children were born dead, 5 children died within early hours and days after delivery due to microcephaly (n=2), brain edema (n=3), cardiopulmonary deficiency (n=1), trauma not associated with delivery (n=1). Recurrence of HL after childbirth occured in 24 (8,6%) women. Twenty three of them had partial or complete remission for less than 2 years, one woman being in complete remission gave birth to a child 5 years after treatment. *Conclusions.* Pregnancy takes its normal course and doesn't cause relapse of HL in most cases in at least 2 years after treatment.

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GLUT1 EXPRESSION PATTERNS INDICATE DIFFERENT WAYS OF GLUCOSE METABOLISM IN HODGKIN LYMPHOMA SUBTYPES AND CORRELATE WITH THE REACTIVE B CELL CONTENT

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A hallmark of malignant tumors is high glucose consumption and an increased glycolytic activity, called the "Warburg effect", which allows staging of cancers with 18F-fluorodeoxyglucose positron emission tomography (PET). Hodgkin lymphoma (HL) is one of the most frequent lymphomas in the Western world and shows high glucose uptake in PET. The aim of this study was to analyze in HL the expression of proteins playing a role in the regulation of glucose metabolism, such as glucose transporter 1 (GLUT1) and lactate dehydrogenase A (LDHA). Immunohistochemical data were compared to PET data. Membrane bound GLUT1 expression was present in the tissue almost exclusively in the Hodgkin- and Reed-Sternberg (HRS) cells and was found in 28 of 41 classical HL (68%) versus 2 of 13 nodular lymphocyte predominant HL (15%). Interestingly, a statistically significant inverse correlation between GLUT1 expression in the HRS cells and the B cell content in the tissue was observed. PET data, available in eight patients, additionally showed a significant correlation between FDG uptake and immunohistochemical GLUT1 expression in the tumor cells as well as a significant inverse correlation to the B cell content in the tissue. Cytoplasmic LDHA expression was observed in 28 of 54 HL (52%), mainly classical HL. The study shows that immunohistochemical GLUT1 expression is a valid marker for glycolytic activity of HRS cells in classical HL and that it correlates with PET data and B cell content in the tissue.

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RARE INFECTIONS IN PRIMARY HODGKIN'S DISEASE

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Introduction. It is well known that patients with HD have an altered immunity and are susceptible to infections, mainly bacterial, often related to treatment induced neutropenia. Rare infections are more common for pretreated cases.We present three cases complicated by uncommon infections and their unusual sites during the first line treatment. Case 1. A 25-year-old man was diagnosed with classical (c) HD stage IIIBX and treated with escalated BEACOPP. After 6th course he developed febrile fever. CT scan revealed new infiltrations on both sides. Microscopy of bronchoalveolar lavage (BAL) fluid showed acid-fast bacili, tuberculosis was confirmed by BACTEC. Chemotherapy was stopped and treatment for tuberculosis was given for 6 months with complete clinical and partial radiological response. During the last follow up visit 12 months after treatment, there were no signs of lymphoma progression but he still had residual tuberculosis on CT. Case 2. A 34-year-old man with cHD stage IIBX was treated with escalated BEACOPP. On 6th course he complained of low grade fever, lasting from the previous course. Chest CT showed local infiltration resembling aspergilloma, BAL fluid was possitive for galactomanan. He was treated with oral pozaconasol for 6 weeks with complete dissapearance of aspergilloma. Baseline BEACOPP without prednislone was given, but due to severe myelotoxicity treatment was stopped. Because of large residual mediastinal mass, PET scan was performed, showing slightly increased FDG uptake in the lower part of the mass. Diagnostic biopsy performed, histology without signs of malignancy. Case 3. A 37-year-old woman with cHD stage IVBX after second escalated BEACOPP course started complaining of left coxalgia and febrile fever, following filgrastim injections. She selftreated with antibiotics and ibuprofen without symptoms improvement. MRI confirmed left coxitis. Surgical procedure revealed purulent coxitis. Following surgical drainage and broad spectrum antibiotic treatment, rapid improvement was observed.

She was given 6 ABVD courses and involved field radiation. The patient is in remission at the moment. *Conclusions.* Patients with advanced HD and treated intensively should be closely monitored for new symptoms and aggresive prompt differentiation should be applied., keeping in mind possibility of tuberculosis or fungal infection early in disease course.

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CHEMOTHERAPY INDUCED PREMATURE OVARIAN FAILURE DOES NOT NEED TO BE PERMANENT, A CASE REPORT

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Introduction. Premature ovarian failure (POF) is defined as an exhaustion of ovarian function before the age of 40. Hormonal substitution is the principal approach to POF treatment. To achieve pregnancy, *in vitro* fertilization is required using donated oocytes. Ovarian damage induced by oncology treatment is among the most frequent causes of POF. *Material and methods.* We present a case of 28-year old woman suffering from POF due to chemotherapy of the Hodgkin lymphoma (HL) who became pregnant spontaneously during hormonal substitution treatment. *Case report.* A young woman was diagnosed with HL in September 2006. The condition was identified at the clinical stage IIB and treated with 4 cycles of ABVD chemotherapy. During chemotherapy, the patient was treated with gonadoliberine analogues (GnRH-a) to prevent development of POF. Unfortunately, HL relapsed after nearly a year (August 2007) required treatment with salvage (DHAP regimen) and subsequently high-dose chemotherapy (BEAM regimen) with autologuous stem cell transplantation. This treatment resulted in POF despite supportive concomitant treatment with GnRH-a. The patient was treated with combined hormonal replacement therapy from May 2008. Two years after the second line oncology treatment, the patient became pregnant spontaneously. Considering the anamnesis of her own 2 healthy children, she decided to undergo termination of her pregnancy. *Discussion and conclusion.* Chemotherapy accelerates atresia of the ovarian follicles. The exact mechanism of its gonadotoxic effect is unknown. POF develops due to the loss of all ovarian follicles containing fetal cells and the likelihood of spontaneous conception is very low. Animal studies have demonstrated the possibility of neo-folliculogenesis of fetal cells from pluripotent bone marrow stem cells, which migrate into the ovary. The case of spontaneous conception described above contradicts the theory of predetermined number of fetal cells in woman´s ovary. Our case report demonstrates that POF induces by chemotherapy does not need to be permanent.

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VARIATIONS OF CLINICOPATHOLOGICAL AND SURVIVAL CHARACTERISCTICS IN HODGKIN-LYMPHOMA IN HUNGARY

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Background. More reports show changing of the Hodgkin lymphoma's (HL) clinocopathological and survival features recently. *Aim.* Examination the characteristics of our HL patients retrospectively. *Patients and methods.* We examined 439 HL patients, who were treated between January of 1980 and December of 2008. *Results.* In the first period (1980-89) were 177 patients, 1990-99 (second period) were 147 patients, and between 2000-08 (third period) were 115 patients. We observed a reduced male-to-female ratio (I. period: 1,42, II. period: 1,45, III. period: 1,04). The mean age was 40,1 years, 35,9 years, and 36,8 years (I. v. II. v. III. period). Comparing the distribution of HL cases diagnosed at 3 different time periods, we detected decreased frequency of the mixed cellularity subtype (43,5%, 58,5% v. 42,6 % P<0,0098), and an increased frequency of the nodular sclerosis subtype (24,85%, 27,2% v. 34,78% P<0,1734). We diagnosed more early stage patients (33,33%, 30,6% v. 59,12% P<0,0001), than advanced stage (66,67%, 69,38% v 40% P<0,0001). From the first symptom (lymphadenomegaly and/or complain) until the diagnosis of the disease lasted an average 6.2 months in the first period. In the second period this only took 4.2 months and only 2.6 months in the third period. Five-years overall survival were 68,4%, 73,3%, and 91%. *Conclusions.* The comparsion of HL cases from the same geographic are during different time period provides an opportunity to observe the changing of clinicopathological features of HL.

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NEW INSTRUMENT FOR COMPREHENSIVE SYMPTOM PROFILE ASSESSMENT IN HODGKIN'S LYMPHOMA PATIENTS: APPLICABILITY AND CHARACTERISTICS

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Comprehensive assessment of symptoms during and after treatment in Hodgkin's Lymphoma (HL) patients is of great value. The goal of this study was to test the applicability of a new symptom assessment tool – Comprehensive Symptom Profile in Lymphoma Patients (CSP-Lym) in patients with HL. CSP-Lym is being developed to assess the severity of 45 symptoms specific for lymphoma patients. It consists of numerical rating scales, scored from "0" (no symptom) to "10" (most expressed symptom). Six clusters of symptoms have been identified, which were clinically relevant and increased the practicability of the tool. Applicability of CSP-Lym in HL patients with preliminary analysis of psychometric properties was tested in a pilot study. 47 HL patients (Stage I-II, n=34; Stage III-IV, n=13) were included in the study. Mean age was 28.7 years old; male/female distribution –16/31. The utility of CSP-Lym was demonstrated: all the items were easy for the patients to read and understand; the data produced by the tool were clear for interpretation by physicians and were used by them in clinical decision making. Reliability of CSP-Lym was satisfactory (Chronbach's alpha coefficient varied from 0.74 to 0.94). The construct validity of CSP-Lym was proved by factor analysis and "known-group" comparison. Statistically significant differences (P<0.05) in symptom severity were found in the groups with/without B symptoms: 60% of symptoms were more severe in patients with B symptoms as compared with the group without B symptoms. Sensitivity to changes was demonstrated by comparison of symptom severity before and after treatment. Thus, CSP-Lym is an appropriate and practical tool to assess the symptom severity in patients with HL. The utility of the questionnaire was shown; preliminary psychometric properties appeared to be satisfactory. Further studies are needed before the wide-spread use of CSP-Lym in clinical practice and clinical trials in this patient population.

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IS INTENSIFICATION OF THERAPY IN HL PET2+ PATIENTS REALLY USEFUL?

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Background. As reported from recent studies, PET2- in patients with HL is an important prognostic factor and a positive predictive value for survival. In order to analyze the feasibility of a prospective randomized study based on early intensification we evaluated retrospectively the outcome of HL pts with PET2+ treated with ASCT as intensification compared with a group of patients conventionally treated. The characteristics of the two groups of patients were homogeneous in terms of clinical features and risk factors. *Methods.* Fifty-seven pts with Hodgkin Lymphoma (HL) and a PET2+, from different Italian centres, were examined: 23 M and 34 F, median age 36 yrs (range 17-77); Hystological types: 44 pts SN, 6 pts MC, 5 pt classical type, 1 pt LP and 1 pt PTS; 16 pts stage IIA and 41 stage IIB-IV. Thirty-one patients (54%) underwent ASCT: 10 pts have undergone ASCT during first-line or immediately after the end ("early"), 21 pts underwent ASCT after at least 3 months from the end of therapy. Twenty-six pts (46%) did not receive an intensification with ASCT: 16 pts were in CR at the end of 1st line therapy, 5 pts were in RP

and 5 pts were in PD. Results: Eight out of the ten patients that underwent "early" ASCT are alive in CR (80%) and two pts (20%) are dead in progression. Twenty-one pts were transplanted as salvage therapy; eleven of them (52%) are currently in CR, 1 is in PD (5%), two are in MR (10%) and seven are dead in PD (33%). The current status of the 26 pts who did not receive ASCT is the following: 18 pts are in CR (68%), 2 pts are in RP (8%), 2 pts are in PD (8%) and 4 pts are dead in progression (16%). *Conclusions.* Our data show that the "early" ASCT has an advantage in terms of achievement of remission. A large randomized study to understand if early ASCT is necessary for all pts with HL and PET2+ is really mandatory.

(On behalf of Intergruppo Italiano Linfomi IIL).

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THE USE OF FDG POSITRON EMISSION TOMOGRAPHY (FDG-PET) IN PATIENTS WITH HODGKIN LYMPHOMA (HL) IN THE "REAL WORLD": A POPULATION BASED STUDY FROM NORTHERN ITALY

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Background. We conducted a population based study to assess how FDG-PET is currently used in patients with HL. *Patients And Methods.* Four Cancer Registries from northern Italy (Modena, Ferrara, Parma and Reggio Emilia) were used to identify patients with HL diagnosed from 2006 to 2008. The study was limited to HIV negative adult patients (Age 18 to 75 years). CT and PET scans were collected before treatment start (B), at the end of treatment (F) and during treatment (I) and were coded according to local report. *Results.* One hundred and thirty six patients out of 185 patients initially collected were identified as study population. M/F ratio was 1.06 and median age was 38 years. Fifty-seven per cent had advanced disease and 13% were enrolled in a clinical trial. Overall, 324 PET scans were performed that correspond to an average of 2.38 scans per patient (2.51 if calculated for patients with at least one PET). B-PET, I-PET and F-PET were performed in 112 (82%), 89 (65%) and 116 (86%) patients, respectively. I-PET was more frequently performed in patients enrolled in a clinical trial (P=0.001) and in those with advance disease (P<0.05). I-PET was coded as positive in 16% of cases, 11% and 19% of patients with early or advanced disease, respectively (P=0.5). No laboratory or clinical parameter was predictive of I-PET results. F-PET was positive in 13% of cases, 0% and 22% of patients with early or advanced disease, respectively. The 3-year overall survival (OS), 3-year relapse free survival (RFS) and 3-year failure free survival (FFS) were 92%, 90% and 73%, respectively. I-PET result was prognostic factor for FFS (HR 5.33: IC95% 2.23-12.8) and RFS (HR 18.2: IC95% 3.32-99.5) but not for OS. F-PET result was the only prognostic factor for OS (HR 14.2: IC95% 3.25-61.8). *Conclusions.* FDG-PET is widely used for patients with HL also outside clinical trials. The prognostic role of I-PET result for FFS and RFS is confirmed also in the real world; in addition, result of F-PET can be used to predict OS.

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BASELINE AND DYNAMIC PROGNOSTIC FACTORS IN NEWLY DIAGNOSED CLASSICAL HODGKIN'S LYMPHOMA

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Introduction. Classical Hodgkin's lymphoma (HL) is a highly curable disease; nevertheless a minor but not negligible part of patients (pts) is refractory to treatment or relapses. We retrospectively analyzed 105 consecutive HL pts in the attempt to identify characteristics, both at baseline and during therapy, predicting for outcome in terms of overall survival (OS), event-free survival (EFS) and relapse-free survival (RFS). *Patients and methods.* Median age at diagnosis was 36 years; 46 pts were male. Stage at presentation was localized in 62 pts (59%) and advanced in 43 pts (41%). B symptoms were registered in 45 cases (42,8%), a bulky mass in 30 pts (28,6%) and extra-nodal involvement in 36 pts (34,3%). Pts were treated with 3 to 8 ABVD cycles according to stage and involved-field radiotherapy (RT) was delivered to 24/62 early stage pts (38,9%). Pts underwent interim PET after 2 cycles. Final restaging consisted of both CT and PET. Therapeutic plan was completed irrespectively to interim PET outcome. *Results.* After a median follow-up of 36 months median OS was not reached, while EFS was 80.5 months. Complete response was obtained in 81 pts (77,1%), partial response in 9 pts (8,6%), while stable or progressive disease was observed in 15 pts (14,3%). Presence of B symptoms, bulky mass and extra-nodal disease correlated to RFS (P=0.0314, P=0.0076 and P=0.0058). Interim PET was positive in 10,3% and 32% of localized and advanced stages, respectively. Interim PET positivity showed a borderline correlation with RFS (P=0.057) (Figure 1). No correlation was found between residual mass of any size at final CT and RFS (P=0.746) (Figure 2). RT was associated with longer EFS in early stage pts (P=0.032). *Conclusion.* This analysis confirms the unfavourable prognostic value of B symptoms, bulky disease and extra-nodal involvement at diagnosis of classical HL. Interim PET, even if didn't reach statistical significance in this small cohort, seems to predict EFS. Presence of a residual mass at final CT didn't correlate with RFS, irrespectively to size. Radiotherapy improves early stage pts outcome in a combined modality and should not be omitted outside of clinical trials.

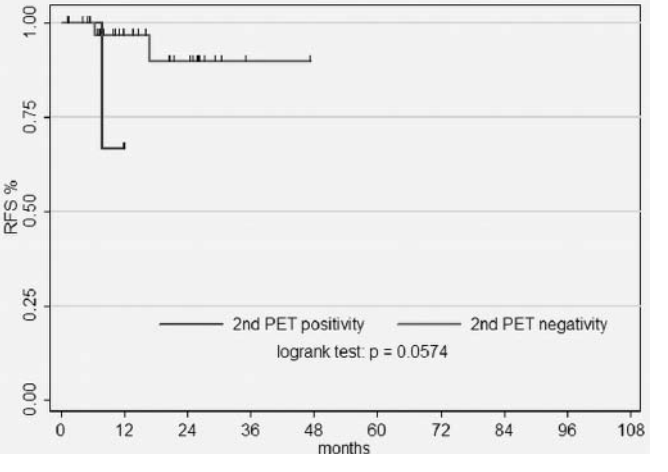

Figure 1. Interim PET positivity and EFS.

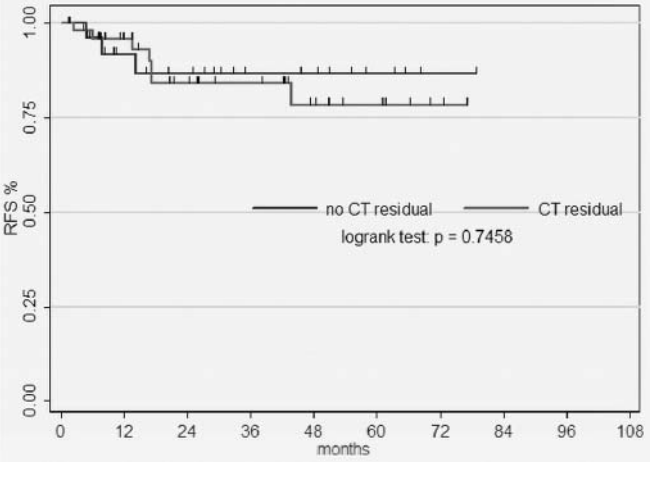

Figure 2. CT residual mass and RFS.

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THIRD TUNISIAN PROSPECTIVE MULTICENTER STUDY FOR ADULT HODGKIN LYMPHOMA (HL) : MDH 2008 PRELIMINARY EVALUATION OF THE RESULTS

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The High rate of relapse: 23% in favorable(fav)advanced HL(IPS<3,treated by 8ABVD)and the adverse prognostic factor of bulky mediastinal mass were the major issues detected in the second Tunisian prospective study (MDH2002). The third prospective study (MDH2008)was opened in july2008 with the main objectives to improve EFS in patients with unfavorableHL(Gr3:stageII with bulky mediastinum,III –IV),to reduce toxicity in patients with favorable HL(Gr1:Fav stageI,II according to EORTC criteria)and intermediate HL(Gr2:Unfav stageI-IIwith no bulky mediastinum). *Patients.* From Jully2008 to December 2009,80eligibles patients(pts) with HL were enrolled to the MDH2008 in four centers.73 pts with median age of 26 years(16-73 yrs)and a sex-ratio of0,78 (32M/41F) were evaluables. Advanced stages were present at diagnostic in 54,2% of cases.68,5% of our pts were B and 38% had a bulky mediastinal mass. *Methods.* Gr1 pts (5,5% of pts) in complete response (CR=response≥75%) after 2ABVD receive 30Gyinvolved field (IF) radiotherapy:RT.If partial response (PR)after initial 2ABVD, pts receive one further ABVD+30GyIF-RT.Pts in failure after initial 2 ABVD receive intensive chemotherapy(CT):2BEACOPP(escalated)+ 30Gy IF-RT. Gr-2 pts (20,5% of pts) in CR after 2 initial ABVD receive 2 further ABVD+30GyIF-RT. If PR after 2 initial ABVD,pts receive intensive CT: 2BEACOPP(esc)+30GyIF-RT. Gr-3 pts(71,2% of pts)in CR after 2 esc BEACOPP receive 6 ABVD. If PR after 2BEACOPP(esc),pts receive 2further esc BEACOPP. If CR after 4 BEACOPP(esc),pts receive 4 BEACOPP(baseline). Pts in PR after 4 BEACOPP(esc) are candidates to intensive CT and autologous stem cell transplantation. Old patients with stages I, II (Gr41,3%) or stages III, IV (Gr5;1,3%) receive respectively 6ABVD+30GyIF-RT and 8 ABVD. We evaluate CR and primary failure rate after 2 cycles of CT and at the end of treatment. *Results.* CR rates were respectively 47% and 90% after 2 cycles of CT and at the end of treatment.Primary failure rate was 10%. At the univariate and multivariate analysis of response according to different prognostic factors,the bulky mediastinal mass was the only adverse prognostic factor concerning response to 2 cycles (CR/CRU: 28,6% vs 60%, P:0.01) and primary failure rate (21,4% vs 2,4%, P:0,014). In Gr3 pts (52 pts), CR rate after 2 BEACOPP (esc), primary failure rate and toxic deaths were respectively of 41%,14% and 7%. *Conclusion.* Compared toMDH2002, the MDH2008 have allowed an improvement of primary failure rate (10% vs 17%) and of toxic deaths rate (7,6% vs 13%). Despite intensive therapy bulky mediastinal mass is still an adverse prognostic factor in our pts.

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MANAGEMENT AND OUTCOME OF ADULT HODGKIN LYMPHOMA (HL) PATIENTS (PTS) IN TUNISIA: PROSPECTIVE MULTICENTRIC TRIAL:MDH2002

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High treatment failure and high number of early relapses in advanced stages were 2 problems detected at the evaluation of the first Prospective trial(MDH 99). To solve these problems,a second version of the prospective trial was elaborated in 2002(MDH 2002). *Patients.* Between 2002 and 2006, 251 eligible HL pts from 6 departments were enrolled in MDH 2002. Median age was 31years(15-70)with 140M and 111F.50% pts had advanced disease,44% had Bulky mediastinum and 69% had B symptoms. *Methods.* MDH2002 strategy was based on the use of the EORTC criteria in early HL and the international prognostic scoring(IPS) in advanced HL,the use of ABVD:3 for favorable(Fav) early HL(G1), 6 for unfavorable(unfav)early HL(G2) and stageIIIA(G3)and 8 for fav advanced HL(IPS<3) and the use of Intensive CT(4 escalated BEACOPP + 4 Baseline BEACOPP) for unFav advanced stages(IPS>2) (G4). 36 Gy Involved field (IF) radiotherapy (RT) was combined to chemotherapy (CT) for early HL and stageIIIA. We evaluate in this study treatment results:primary failure rate, EFS, RFS and OS. *Results.* 40% pts were treated in G2,29% in G4, 17% in G5 and only 9% in G1. Eleven (4.3%) toxic death were observed during treatment including 10 deaths in the 72 pts treated with escalated BEACOPP. Of the remaining pts, 83% had CR and 17% had primary failure at the end of the treatment. 25 relapses (12%) were observed with a median time to relapse of 9 months: 9 (10%) in G2, 6 (8%) in G4 and 10(23%) in G5. 5 years OS, EFS and RFS were respectively 88%, 73% and 88%. In multivariate analysis, the unfavorable prognostic factors emerging were Bulky mediastinal disease for EFS (55% vs 80%, P=0.03) and remission status at the end of therapy which influenced EFS(87% vs 50% vs 5%, P=0.0000) and OS(96% vs 62% vs 55%, P=0.001). *Conclusion.* The high rate of relapse (23%) in fav advanced HL and the adverse prognostic factor of mediastinal bulky disease were the major issues detected in MDH 2002. A new prognostic staging have decided in the third version of the protocol (MDH 2008) including 3 stages: Favorable (Fav early stage), intermediate (unfav early HL with no bulky mediastinal disease) and unfavorable (stageII+ bulky mediastinal disease,stages III-IV). Intensive CT is currently the treatment of all unfavorable HL.

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REDUCTION OF CARDIAC, BREAST, LUNG, ESOPHAGUS, AND TOTAL BODY INTEGRAL RADIATION DOSE WITH PROTON THERAPY IN HODGKIN LYMPHOMA (HL) PATIENTS WITH MEDIASTINAL INVOLVEMENT

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Background. Radiotherapy has been associated with pneumonitis, late cardiac complications and secondary breast and lung cancers in HL survivors. These effects are correlated with volume of normal tissue irradiated and mean dose to each organ at risk (OAR). Retrospective dosimetry studies have shown potential improvements in radiation exposure to OAR with proton therapy (PT). We report a series of patients prospectively evaluated for consolidative PT. *Materials and methods.* Between 2008-2010, 8 HL patients with mediastinal involvement underwent comparative treatment planning for conventional radiation therapy(XRT) and PT with intent to use PT(30-39.6 Gy/CGE) following chemotherapy to all sites of disease if there was a dosimetric advantage for OAR. Treatment planning required 99% of the target volume receive 100% of the dose(CTVD99%=100%). Critical OAR included heart, lungs, breasts(women only-n=7), esophagus and total body.

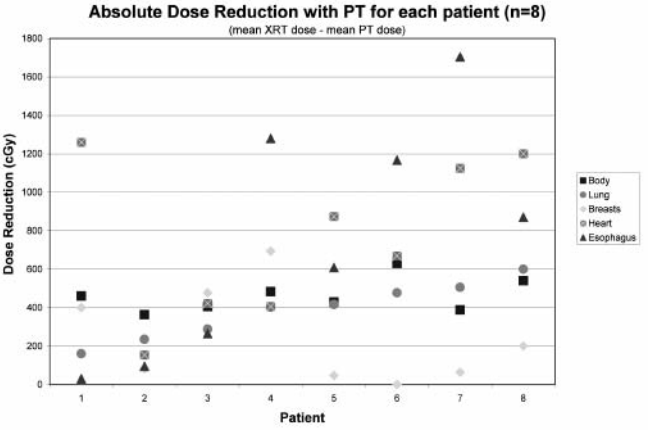

Figure. The graph shows the absolute dose reduction (mean XRT dose – mean PT dose) in mean dose to the critical structures(legend) for each patient (X-axis) with proton therapy. For example in patient 7, PT reduced the mean dose to the esophagus by 17 Gy, but reduced the mean dose to the breast by only 1 Gy. Notice how all the values are positive, indicating that proton therapy reduced the dose for all structures in all patients (except breast dose in patient 6- a male, whom breast tissue was not evaluated = 0).

Results. Mean heart dose with XRT was 16.9 Gy (median) (range 3.6–31.2Gy) compared with 6.9CGE (1.7-19.2CGE) for PT. Mean heart dose was reduced by >4 Gy in 7 patients and >10 Gy in 3 patients. Mean breast dose with XRT was 5.7Gy (2.5-12.1Gy) compared with 5CGE

(1.7-7.4CGE) for PT. PT reduced mean breast dose >4Gy in 3 patients and by 7 Gy in a patient with axillary involvement. Mean lung dose with XRT was 9.8Gy(5.9-16.8Gy) compared with 6.4CGE (3.5-11.7CGE) for PT. In 5 patients PT reduced the mean lung dose by >4Gy and in 2 patients it was reduced by >5Gy. PT also reduced the dose to the esophagus with mean dose of 19.2Gy with XRT and 11CGE with PT. 5 patients had mean esophagus dose reduced by >6Gy and 3 by >10Gy. PT also reduced total body exposure: median relative reduction in volume of body receiving 30 Gy (V30) was 55%; V20, 43%; V10, 37%; and V5, 37%. *Conclusions.* PT reduced dose to critical structures without compromising coverage or dose to target volume. Reductions of >4Gy in mean dose to heart, breast, lung, and esophagus were seen in 7, 3, 5, and 5 patients, respectively. Dose reduction to these organs should result in lower risks of acute pneumonitis and late cardiac disease and secondary malignancies in HL survivors.

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ELEVATED SERUM TARC LEVELS ARE ASSOCIATED WITH PROGNOSIS IN HODGKIN'S LYMPHOMA

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TARC, a protein highly espressed by RS cells and by the microenvironment of HL involved lymph nodes is detectable in the serum of HL patients (pts). In this study we prospectively investigate the prognostic role of TARC serum levels (T) in Classical HL outcome. *Patients and Methods.* Between November 2006 and May 2010, T (pg/mL) was measured by Elisa in 94 pts: 67 untreated pts (Group A) and 27 pts relapsing or progressing after first-line CT± RT (Group B). Group A pts recieved 4 ABVD cycles + IF RT for stage I-IIA, and 6-8 ABVD cycles ± RT on bulky for stage IIB-IV. Group B received 4 cycles of Ifosfamide-containing regimens followed by HDBEAM and ASCT. T were analyzed after each CT cycle, at the end of treatment and during follow-up. *Results.* Main pts characteristics were as follows: M/F:42/52; age ≥45 yrs:17%; NS histology 85%; Stage III-IV:40%; B symptoms: 55%; bulky disease: 53%; extra±nodal involvement:31%; >3involved sites:54%; IPS>2: 15%. Basal T values (T0) >536 were observed in 88% Group A pts and 81% Group B pts (536 was the 95th centile of T distribution in a group of 40 independent healthy subjects). After 2 CT cycles, T values (T2) were significantly lower than T0 in both groups; T2 >536 were detected in 43% Group A pts and in 63% Group B pts. PET-2 scan was positive in 18% Group A pts and in 52% Group B pts. The chance of having a positive PET-2 was similar in pts with T0 >536 and T2 ≤536 compared to pts with T0 ≤ 536 (OR:0.8;95% CI: 0.1-9.5), whereas it was 10-fold greater in pts with both T0 and T2>536 (OR: 10.0; 95% CI: 1.2-85.2). After a median follow-up of 25 months, progression-free survival (PFS) was 78% in Group A and 53% in Group B. PFS was 100% vs 81% vs 54% in pts with T0<536, T0>536 and T2≤536, and both T0 and T2>536, respectively (P=0.012). *Conclusions.* Our study confirms that T at baseline and after 2 Ct cycles may help in predicting PET-2 results and disease outcome.

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COINCIDENCE OF HODGKIN LYMPHOMA AND SYSTEMIC SARCOIDOSIS - DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS

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Objectives. The clinical presentation of Hodgkin lymphoma and sarcoidosis can be similar and may result in a differential diagnostic problem. *Case report.* A 35 year-old female presented with gulp difficulties, has been started to investigate in January 2009, and nodular sclerosing Hodgkin lymphoma (NS-HL) was confirmed with histological examination. The staging PET/CT demonstrated disseminated disease with lung and spleen involvement (clinical stage IV/BS, international prognostic score: 1). After the second ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) interim PET/CT scan was made, which showed an inadequate therapeutic response, therefore rebiopsy was made. The histological examination revealed sarcoidosis. Because of the diagnostic dilemma we decided to remove the infradiaphragmatically most intensively pooling spleen, which showed sarcoidosis but the lack of HL manifestations. The revision of the first histological finding confirmed the diagnosis of HL. We continued the treatment with 4 cycles CHOP-14 (cyclophosphamide, adriamycin, vincristine, prednisolone), with low-dose steroid administration between each cycles. After the second CHOP-14 an interim PET/CT scan was done again, which showed a good response. After four months in complete remission (CR) a local relapse of NS-HL was recognized in the right supraclavicular region confirmed by lymph node biopsy and histological examination, thus involved field irradiation was applied and clinically the patient is in CR again since 5 months. *Conclusions.* Local granulomatosis inflammation related to HL is relatively common and can be detected by histology, while the development of systemic inflammatory reactions are uncharacteristic during the chemotherapy induced immunosuppression. The co-existence of these two diseases may indicate a common immunregulatory disturbance.

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EXPERIENCES OF THE FIRST TWO YEARS WITH INTERIM PET/CT IN HODGKIN-LYMPHOMA - THE HUNGARIAN CHEAP STUDY

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Background. 18FDG-PET/CT after 1-3 chemotherapy cycles ("interim") is predicting prognosis better than any of the available classical prognostic factors. *Patients and methods.* A total of 70 Hodgkin-lymphoma (HL) patients underwent 18FDG-PET/CT after two or three cycles of chemotherapy. We investigated the value of 18FDG-PET/CT for prediction of progression-free survival (PFS) and overall survival. *Results.* We examined 69 patients after two cycles of ABVD and one after the third cycle. The median age of the patients was 38 years. 44 patients had early and 30 advanced stage disease at the time of diagnosis. 33 patients had B signs. 32 patients had negative FDG-PET scans, 11 patients had minimal residual uptake (MRU) and 27 patients had positive scans by the Gallamini definition. There were 2 relapse in the negative group and 11 in the positive group and there was no relapse in the MRU group. 3 patients died in the positive interim PET/CT group. There was significant different between the groups in progression free survival (PFS) (P<0,001) based on the results of interim PET/CT. PFS was 96,3% in the PET negativ group, and 53 % in the PET positive group at 30 months. *Conclusion.* Interim FDG-PET/CT is an useful and independent predictor of PFS in HL. It could be possible to avoid under- and over treatment of patients with used of interim PET/CT.

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INCREASED RISK OF INFECTIOUS COMPLICATIONS IN HIV PATIENTS WITH ADVANCED STAGE AND RELAPSED HODGKIN LYMPHOMA

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Background. Patients with human immunodeficiency virus (HIV) have a 10-fold increased risk of developing Hodgkin lymphoma (HL). Prior to combination antiretroviral therapy (cART) outcomes for HIV-HL patients were dismal. Current studies highlight improved outcomes (Gastaldi, Martino *et al.* 2002; Xicoy, Ribera *et al.* 2007) and show feasibility of intensified therapies including autologous stem cell transplant (ASCT) (Re, Michieli *et al.* 2009). *Methods.* We conducted a retrospective study of HIV-HL patients referred to our institution from 01/1998 to 12/2008. *Results.* Five newly diagnosed and two relapsed patients (5 mixed cellularity, 2 nodular sclerosis) were seen. All were receiving cART. Median age was 42. Three patients died within 3 months of diagnosis. These patients died of septic shock and were unable to receive beyond 1 cycle of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine). All had advanced disease and two had an International Prognostic Score (IPS) of 5. CD4 lymphocyte counts ranged from 53 to 219 per uL and HIV viral load ranged from undectectable (below 50 copies/mL) to 71,500 copies/mL. Two patients remain in complete remission (CR) after ABVD with progression-free survival (PFS) of 13 and 99 months. Both had CD4 counts greater than 285 and undetectable HIV viral loads. Two patients presented with relapsed disease. One patient had an initial PFS of 55 months, B symptoms, extranodal disease, CD4 of 340 per uL, and an undetectable viral load. He then underwent an ASCT in a second CR.

After repeated bacterial pneumonias he died 7 months after ASCT from multi-organ failure and disease relapse. A second patient had an initial PFS of 12 months, B symptoms, extranodal disease, CD4 of 130 per uL, and an undetectable viral load. He underwent 4 lines of salvage chemotherapy and radiation for management. He did not undergo ASCT because of refractory thrombocytopenia and repeated infections. He died 37 months after relapse from a myocardial infarction. *Conclusion.* Challenges remain in the management of HIV-HL patients. In our series those with advanced stage disease, high IPS, and low CD4 counts had short survivals. Also risks of cytopenias and infections are pronounced during relapsed treatment even with growth factor support.

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PENCIL BEAM (PB), COLLAPSED CONE (CC) AND MONTE CARLO (MC) DOSE CALCULATION: DIFFERENCES IN DOSE DISTRIBUTION IN THE TREATMENT OF MEDIASTINAL HODGKIN LYMPHOMA (HL) AS A CONSEQUENCE OF USING DIFFERENT ALGORITHMS

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Introduction. The dose distribution in a radiation treatment plan depends on the chosen algorithm particularly when treating inhomogeneous tissue. Of all patients with HL the heterogeneous mediastinal region is involved in up to 30%. In this study, we analyze the differences in dose distribution in the treatment of mediastinal HL between PB and CC for 3D-Radiotherapy (3D-RT) and between PB and MC for IMRT. *Methods.* We created 3D-plans (ap-pa) and IMRT-plans (9-11 beams) for 20 patients with mediastinal HL and used both PB and CC for 3D-RT, and both PB and MC for IMRT. Prescription dose was 30 Gy as the median PTV-dose. Dose-volume-histograms were created for all plans. For the PTV we analyzed mean dose, Conformity Index (CI) and Homogeneity Index (HI). Regarding the organs-at-risk we analyzed V4 and V25 for the heart, V10 and V20 for the lungs and V10 for both breasts. *Results.* For the comparison PB/CC (3D-RT) and PB/MC (IMRT) the mean PTV dose (in Gy) was 29.89/29.68 and 29.94/29.75, CI was 2.77/2.77 and 1.28/1.25 and HI was 0.85/0.82 and 0.84/0.77. For the heart V4 (in %) was 73.04/74.77 and 87.75/94.18, while V25 (in %) was 49.94/49.58 and 14.08/12.35. For the lungs V10 (in %) was 35.56/37.73 and 54.84/58.52, and V20 (in %) was 28.68/27.77 and 20.09/15.97. For the breasts V10 (in %) was 16.43/17.13 and 19.08/15.97 (left), respectively 7.81/7.85 and 14.84/10.45 (right). For 3D-RT all differences were statistically significant (p less than 0.05) except PTV-CI and breasts-V10, for IMRT all except PTV-CI. *Discussion.* Mean-PTV-dose and conformity are not affected by different algorithms (the 0,2Gy-difference for mean dose can be considered clinically irrelevant); more heterogeneity is seen with both CC and MC. While V10 for the breasts in 3D-RT is not affected at all, both CC and MC calculate higher values for low doses (V4&V10) and lower values for high doses (V25&V20) of the heart and the lungs. Known differences between "dose to water/medium" calculations explain partially these differences. In conclusion, there are noticeable differences in dose distribution dependent on the chosen algorithm, particularly for IMRT, which should always be considered when analyzing treatment plans.

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MODERN TREATMENT OF MEDIASTINAL HODGKIN LYMPHOMA (HL): ADVANTAGES OF INTENSITY-MODULATED RADIATION THERAPY (IMRT) AND/OR INVOLVED NODE TARGET VOLUME (IN) COMPARED TO CONVENTIONAL 3D-RADIOTHERAPY (3D-RT) AND INVOLVED FIELD TARGET VOLUME (IF)

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Introduction. The major problems for HL survivors are late damage to heart and lungs and second malignancies. In this study we analyze to what extent IMRT and/or IN can reduce exposure for the organs-at-risk (OARs) in the treatment of mediastinal HL when compared to the standard approach (3D-RT and IF). *Methods.* We calculated both 3D-plans (Collapsed-Cone) and IMRT-plans (Monte-Carlo) for both IF and IN based on the CT-data of 20 patients with mediastinal HL. The prescription dose was 30Gy as the median dose in the PTV. Dose-volume-histograms were created for all plans. For plan quality we analyzed Homogeneity-Index (HI) and Conformity-Index (CI) for the PTV. Regarding the OARs we analyzed V4 (heart), V20 (lungs) and V25 (breasts), beside mean dose for all. *Results.* Comparing 3D-RT and IMRT in either IF/IN, HI was 0.82/0.85 and 0.77/0.78 and CI was 2.77/2.80 and 1.25/1.24 for "3D IF/IN" and "IMRT IF/IN", respectively. The mean-heart-dose (in Gy) was 17.94/9.19 and 13.76/7.42, while V4 (in %) was 74.77/39.52 and 94.18/50.35. The mean-lung-dose was 10.62/8.57 and 12.77/9.64 and V20 was 27.77/21.87 and 15.97/11.25. The mean left breast dose was 4.37/3.42 and 2.30/1.63, while V25 was 3.78/3.26 and 0.67/0.64. The mean right breast dose was 6.04/4.59 and 5.37/3.53, and V25 was 0.75/0.61 and 0.25/0.18. Comparing 3D-RT vs. IMRT, all differences were statistically significant (p less than 0.05) except mean-heart-dose (IN-plans) and V25 for the right breast (IF-plans); comparing IF vs. IN, only differences for CI (3D-plans) and V25 for both breasts (3D&IMRT-plans) were statistically insignificant. *Discussion.* While increasing dose heterogeneity in the target, IMRT achieves better conformity with subsequent reduction of mean-heart-dose and of high doses to lungs and breasts. Disadvantage of IMRT was increased exposure of low doses to the heart, lungs and breasts. Targeting IN instead of IF-PTV can improve all relevant OAR parameters except for high doses in the breasts and mean-heart-dose. In conclusion, both IMRT and target volume diminution should lead to reduction of late organ damage in HL survivors. The minor increase in mean lung and breast dose should be weighted carefully against the benefits of IMRT especially when second malignancies are considered.

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HODGKIN'S LYMPHOMA OF THE SKIN: REVIEW OF THE LITERATURE AND CASE REPORT

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Introduction. The localization of Hodgkin's disease (HD) on the skin is unusual and frequently occurs late in the course of the disease. It manifests with single or multiple dermal or subcutaneous nodules. Direct extension from an underlying nodal focus, hematogenous dissemination, and most often, retrograde lymphatic spread, distal to involved lymph nodes, are the mechanisms usually implicated. *Case report.* We report the case of 85 years old woman who developed Hodgkin's lymphoma with cutaneous involvement. She accused malaise, fatigue and loss of weight. On physical examination the unilateral supraclavicular lymph node was found (diameter 2.0 cm) and ulcerated lesion of the neck of 5 cm diameter. The remaining of physical finding was normal. Laboratory data revealed only a high value of LDH. Total body scan was negative. The biopsy of lymph node reveled Hodgkin's lymphoma, mixed cellularity subtype. The PET total body after node biopsy showed a single area with excavation at the canter at the level of subcutaneous tissue in the left occipital (SUV max 5.9). The skin biopsy pointed a dermal localization of Hodgkin's lymphoma, $CD30^+$ and $CD15^+$. Histology of bone marrow was normal. The patient was considered in clinical stage II AE and was treated with three cycles of VEPEMB protocol and with RT/IF. Actually the patient is in complete remission after six month after the end of treatment with negative PET imaging. *Discussion.* Primary cutaneous HD is very uncommon and usually represents a rare late manifestation of dissemination of the disease heralding a severe prognosis. Specific skin lesions were described in 3.4-7.6 % from all cases of HD and have been categorized as papules, nodules, plaques or infiltration, ulcerative lesions, a combination of these, and erythroderma and often are accompanied by pruritus. The skin of the chest seems to be most frequently involved. Recently, cutaneous HD has been described in patient with human immunodeficiency virus infection. *Conclusion.* The skin is involved usually in advanced HD and often portends an ominous prognosis; however, it also might follow a relatively benign course, and more and more intensive systemic chemotherapy sometimes is effective in such cases.

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HODGKIN'S LYMPHOMA (HL) IN ADOLESCENTS TREATED WITH PEDIATRIC PROTOCOLS: A REPORT FROM THE ITALIAN ASSOCIATION OF PEDIATRIC HEMATOLOGY AND ONCOLOGY (AIEOP)

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Since 1996 age eligibility in the therapeutic protocols for HL in childhood was raised to 18 years. Objective of our study is to compare characteristics, risk factors and prognosis of adolescents (≥15-18 yrs) and children registered in the 2 subsequent protocols AIEOP MH'96 and LH2004, which plan 3 ABVD + RT or 4 or 6 COPP/ABV + RT for the 3 therapeutic groups. 207 adolescents were registered, 91/560 (16.25%) in MH'96 and 116/435 (26.7%) in LH2004 study. 102 pts (49.3%) were female, 86 pts (41.5%) presented with B-symptoms and 99 (47.8%) had large mediastinum. The pediatric population included 788 pts, 469 registered in MH'96 and 319 in LH2004 protocol. 328 (41.6%) were female and 266 (33.7%) presented B-symptoms. Bulky mediastinal mass was present in 342 (43.4%) pts. The most common histological subtype in adolescents was NS (168=84% vs 537=69.6%), but MC (19=9.1% vs 135=17.5%) and LP (11=5.5% vs 86=11.2%) were more frequent in younger pts. Only histology and symptoms were statistically different in the two groups of pts (Z test). Compared to pediatric population, adolescents showed similar prognosis in both protocols. The 12-yrs OS in MH'96 study is 91.5% and 90.2% and the 12-yrs Freedom From Progression (FFP) is 81.4% and 81.1% for children and adolescents respectively. The 5-yrs OS registered in LH2004 protocol is 95.2% and 95.1%; the 5-yrs FFP is 78.6% and 90.6% in <15 and ≥15 yrs old pts respectively. Frequently, adolescents are included in adult protocols, or not included in clinical trials at all. In literature no prospective randomized study compares prognosis of adolescents with that of younger children or adults. Similarly to most of pediatric clinical trials, in our study adolescence appears as a non significant prognostic factor. Considering that analogous results are obtained with adult HL protocols, it could be more difficult to decide the best therapy for this category of pts. Since pediatric protocols are heavily modulated to reduce long-term side effects, we believe they are the best therapeutic option.

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ROLE OF ULTRASONOGRAPHY (US) IN DIFFERENTIAL DIAGNOSIS OF MEDIASTINAL MASS ENLARGEMENT AFTER THERAPY OF PATIENTS WITH ADVANCED STAGES OF HODGKIN DISEASE (HD) TREATED BY BEACOPP-14 CYCLES WITHOUT SUBSEQUENT IRRADIATION

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Introduction. We have treated 45 patients with advanced stages of HD with mediastinal involvement by 6 cycles of BEACOPP-14 during 2007-2009 years.Taking into account small residual mass (<2 cm by CT) patient were not subsequently irradiated. In the time from 1 to 10 months we revealed asymptomic soft tissue mass enlargement in the region of previously regressed tumour in 13 of the patients (29%). Medical visualization technics were applied with 1-3 months periodicity. *Materials and methods.* US is a routine diagnostic tool used in our clinic for lymphatic tumours monitoring, including that of mediastinal localization. At this work it was applied for distinguishing of lymph node fibrosis, disease progression and thymic enlargement in 12 of 13 patients. *Results.* All the patients were diagnosed at the age of 19-31, women were 9 of 13 (69%). Enlarged thymus had typical US picture: tiny grainy mass of middle echogeneicity in thin capsule, located in upper mediastinum, well deformed by heart contractions, avascular by color Doppler. Different US picture defined lymph node fibrosis and active tumour progression. Thymomegaly was diagnosed in 8 of 12 patients,1 patient was false negative by US, 2 patients were diagnosed fibrosis only. Progression of disease was suspected in 5 of 12 patients by CT, but nobody of them was confirmed as active tumour after US assessment. Absense of disease progression was additionally confirmed by negative PET scans in 2 patients. Further observations during next 3-12 months showed slight decrease of mediastinal mass size measured by CT and US in concord. *Conclusion.* US of mediastinum is highly informative diagnostic tool for diagnosis of thymus enlargement and exclusion of HD progression in the patients of above described group with sensitivity to nature of the process higher than CT.

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HODGKIN LYMPHOMA AS RICHTER'S TRANSFORMATION OF CLL

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Richter's transformation occurs in 5% of patients with chronic lymphocytic leukemia (CLL) and denotes the development of high-grade non Hodgkin lymphoma, prolymphocytic leukemia, Hodgkin lymphoma (HL)(0.4%), or acute leukemia. We present two cases of HL occurring in patients treated for CLL. On August 2002 a 67 years old woman was treated for CLL stage B by alkylant without any clinical response. On April 2005 she presented a rapidly enlarging of axillary lymph nodes with fever. Lymphadenectomy confirmed the diagnosis of HL $CD30^+$, $CD15^-$, $CD20^+$. Reed Sternberg cells are presented in a typical polymorphous inflammatory background. She was treated for his HL stage II Bb by combined chemo-radiotherapy. One year later she presented a splenomegaly with lymph nodes. The biopsy revealed a diffuse large cell lymphoma $CD20^+$. The second case is about a 56 year old male diagnosed since 2005 as CLL stage B. He received 6 monthly cycles of RFC between December 2007 and June 2008. Complete remission was obtained after RFC with normal BOM, normal cytogenetic assesment and normal CT scan. 11 months after the end of RFC, he presented fever, sweats with multiple cervical and axillary lymph nodes and splenomegaly of 10 cm. Blood count was normal. Lymph node biopsy confirmed the diagnosis of HL type 2, $CD30^+$, $CD15^+$, LMP1+, EMA^+, $CD20^-$, $CD3^-$. Bone marrow biopsy was normal. He has HL stage III Bb, treated by 4 cycles of ABVD with failure. He has just received chemotherapy type IGEV. The filiation between CLL and HL exit and the large cells of Richter's syndrome may arise through transformation of the original CLL clone or represent a new neoplasm. The incidence of HL secondary to CLL is not well determined. The origin of Hodgkin-Reed Sternberg like cells is the germinatif center and it seems to be the precursor of Reed Sternberg cells in Hodgkin lymphoma. Molecular study of clonality is necessary to determine the relationship between CLL clone and HL clone in our patients. The treatment is not different to that of HL *de novo* but the prognostic seems to be less good than HL *de novo*.

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CLINICAL CHARACTERISTICS AND TREATMENT RESULTS OF PEDIATRIC HODGKIN LYMPHOMA: A SINGLE INSTITUTION EXPERIENCE

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Purpose. To evaluate the clinical characteristics and treatment results of pediatric Hodgkin lymphoma population in Tunisian haematology department. *Patients and Methods.* A retrospective study was carried out from 1991 to 2010. All patients aged under than 15 years old with newly Hodgkin lymphoma diagnosis are included in this study. *Results.* 24 patients were referred. Median age was 9.5 years with a male: female ratio of 1.8. Histologic subtype 2 and 3 were the most frequent. 8 lacked full immunophenotyping. CD30 is positive in 100% of cases, CD15 is positive only in 13 among 16. CD 20 is + in 3 cases among 4. Advanced stages (III, IV) were present at diagnosis in 62.5%. 46% were B and all were b. one third of A lymphoma were b. 62.5% of patients had more than 3 involved areas. 16.7% of cases had extranodal disease (liver, bone marrow and bones). 15% were with Bulky mediastinal disease and 12.5% with peripheral bulky disease. All patients were initially treated by chemotherapy. It consisted of 4 or 6 cycles of OPPA/VBVP/COPP/ABV/MINE. 78.3% of patients received radiotherapy within an average time of 1.9 months. In two third of them radiotherapy concerned involved fields. The overall response rate after

chemotherapy is 91.6 %. Radiotherapy was induced improvement of response in 50% of patients. 2/24 relapsed within 13 and 24 months after the end of treatment. The median overall survival is 48.5 months. The 5 year relapse free survival is 88%. These results are encouraging. Actually the majority of pediatric HL has an excellent chance of definite cure but the goal is to minimize long term side effects.

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IMPACT OF CENTRALISED MULTIDISCIPLINARY EXPERT RE-EVALUATION OF DIAGNOSTIC PROCEDURES IN PATIENTS WITH NEWLY DIAGNOSED HODGKIN LYMPHOMA

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Background. Hodgkin Lymphoma (HL) is highly curable when treated accurately. Long-term side effects, such as secondary tumours and cardiovascular diseases, are related to the intensity of treatment. International efforts aim at minimizing side effects without compromising the cure rate. Treatment reduction can be based on pre-treatment risk factors and early treatment response but asks for accurate initial staging. Therefore, we offer the non-academic hospitals in our Comprehensive Cancer Centre East-Netherlands (IKO) collaboration network, a centralised review of all diagnostic procedures for patients with newly diagnosed HL. Here, we report on our first evaluation of this approach. *Patients and methods.* Patients are referred to the RUN-MC outpatient clinic and jointly seen by haematologist and radiation oncologist. In the weekly multidisciplinary meeting together with expert pathologists, radiologists and nuclear medicine physicians, all diagnostic information is reviewed and treatment advice formulated. The treatment is mostly given at the referring hospital. Data of all patients referred between February 2006 and May 2009 were collected from paper and electronic patient records. CT-, FDG-PET/CT-scans and histological biopsies were reviewed. Discordant revisions in histopathology, staging and/or therapy were recorded as 'minor', having no therapeutic consequences, or 'major', resulting in adapted therapeutic advice. *Results.* In total 97 patients were included, representing 95% of all newly diagnosed patients in our region. Histopathology review showed a concordance rate of 82%; in 12% minor discordance (all within subtyping of cHL); in 6% major discordance: nodular lymphocyte predominant HL (NLPHL) change to lymphocyte-rich classical (LRCHL), n=2, vice versa, n=1, NLPHL change to diffuse large B-cell (DLBCL), n=1, doubtful NHL/HL change to cHL, n=1, non-classifiable lymphoma to cHL, n=1. Revision of initial staging was completely concordant in 59% and minor discordant in 25%. Nine patients were upstaged from CSII to CSIII/IV, one patient downstaged from CSIII to CSII. The changes in histopathology and staging led to an overall major change in treatment advice in 17 patients (17.5%). *Conclusion.* Central review of diagnostic workup for patients with HL led to a significant percentage of major discordances between the referring hospital and centralised expert opinion. Individual patients may benefit from this centralised experience.

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HODGKIN'S LYMPHOMA (HL) IN THE PORTUGUESE POPULATION – EPIDEMIOLOGICAL AND PATHOLOGICAL CHARACTERIZATION

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The epidemiology of classical HL (cHL) in Portugal, an European country with an elevated number of immigrants from West Africa, is unreported. We determined the histological distribution and sex and age-specific incidence of HL in the Portuguese population and compare it to the European pattern. For that, we retrospectively analysed all cases registered at the Portuguese Cancer Registry-South Region (a network comprising 29 hospitals representative of the country's epidemiology) between 1999-2003 and determined the sex and age-specific incidence and exact 95% confidence intervals. To investigate a possible recent trend for higher incidences in older ages, we used the Standardized Incidence Ratio (SIR) for comparison between 2006-2007 and 1999-2000. 615 cases were diagnosed in the south of Portugal between 1999 and 2003, with a male/female ratio 1.24:1. The age specific incidence revealed a bi-modal distribution with two peaks: 15-24 yo (4.41/100 000 inhabitants) and 65-74 yo (2.94/100 000/inhabitants). The incidence above 55 yo in 1999-2000 and 2006-2007 (3.56 and 3.81 in men, respectively, and 1.89 and 2.87 in women, respectively) increased by 25% (SIR:1.25, 95% CI:1.02-1.52, P=0.03 two-sided Mid-P exact test). This was attributable to an increased incidence in women older than 55 (SIR:1.50; 95% CI:1.12-1.99, P=0.007), whereas in men the incidence remained stable (SIR:1.07, 95% CI:0.80-1.41, P=0.60). Since the registry data included histology in only 73% cases, we reviewed the histology of 229 consecutive patients (median age 29 and 40.5 yo, respectively, P<0,001 Mann-Whitney test, and a similar male to female ratio) diagnosed in our tertiary cancer care center between 1999 and 2003. These patients were younger than patients in the network hospitals. 92% were subclassifiable, with 5% nodular lymphocyte predominance and 95% (199 cases) cHL. Nodular sclerosis accounted for 89% and mixed cellularity for 6.5% of cHD cases. In Portugal, where immigration from African countries could have lead to different disease characteristics, epidemiology of HL is similar to Europe. Similarly to other western countries, we observed a trend for an increased incidence in the elderly. A higher than expected proportion of nodular sclerosis was found in a subgroup analysis, may be related to the younger age in this subgroup.

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IMMUNOHISTOCHEMICAL EXPRESSION AND PROGNOSTIC SIGNIFICANCE OF THE PROLIFERATION MARKERS MCM2, MCM7 AND CYCLIN D3 (CCND3) IN HODGKIN LYMPHOMA

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Background. Several biological markers have been associated with HL patients' prognosis. Increased proliferation rate of Hodgkin/Reed-Sternberg (HRS) cells may be associated with inferior outcome, but this issue still remains controversial. Minichromosome Maintenance Proteins (MCMs) are essential for the initiation of DNA replication; D–type Cyclins catalyze progression through the G1/S restriction point. *Purpose.* To evaluate CCND3, MCM2, MCM7 and Ki67 expression by HRS cells and investigate its correlation with demographic, clinical, laboratory and histopathological parameters, as well as the outcome of HL patients. *Patients and methods.* Lymph node sections from 138 HIV–negative HL patients, >14 years old (93% treated with ABVD or equivalent regimens), were immunohistochemically stained for CCND3, MCM2, MCM7 and Ki67 and evaluated by image analysis. *Results.* MCM2 was expressed in 115/116 cases in a median of 63% of HRS cells; MCM7 in 121/121 cases, median 88%; CCND3 in 105/113 cases, median 24%. MCM2 and MCM7 were interrelated (Spearman's rho 0.28, P=0.004), but were not correlated with CCND3 or Ki67. Higher MCM2 expression was observed for patients with early stages (P=0.03), lower leukocyte counts (P=0.03) and higher albumin levels (P=0.002); higher MCM7 expression for asymptomatic patients (P=0.004), early stages (P=0.005), <5 involved sites (P=0.009), no anemia (P=0.02) and higher albumin levels (0=0.005); higher CCND3 expression for older patients (P=0.03), lower leukocyte counts (P=0.05) and normal LDH (P=0.05). No correlation with failure free (FFS) or overall survival (OS) was found in univariate analysis for any of these markers. Multivariate analysis revealed that high MCM7 expression (analyzed as a continuous covariate) was an adverse prognostic factor for OS along with older age and advanced stage (P=0.045), while of borderline significance for FFS when adjusted for stage (P=0.06). *Conclusions.* HRS cells express MCM2, MCM7 and CCND3 in the vast majority of HL cases. Interestingly, MCM2 and MCM7 expression was lower in patients with markers of more extensive or aggressive disease. For this reason, although not associated with outcome in univariate analysis, higher MCM7 expression emerged as an adverse prognostic factor in multivariate analysis. Thus MCM7 deserves further evaluation as a potential independent prognostic factor in larger patient series.

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COMPARISON OF VISUAL AND QUANTITATIVE ASSESSMENT FOR FDG-PET INTERPRETATION IN HODGKIN LYMPHOMA AFTER 2 CYCLES OF ABVD. THE EORTC-GELA-IIL H10 TRIAL EXPERIENCE

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Background. Recent trials are focused on risk adapted treatment strategies for Hodgkin's lymphoma, using functional imaging of glucose metabolism, fluoro-desoxy-glucose positron emission tomography. Different interpretation criteria for interim PET had been proposed. The purpose of this study was to compare information given by visual analysis to semi quantification. *Methods.* This study was performed on 84 patients with newly histological proven cHL, included between January and May 2008 in the H10 GELA-EORTC-IIL protocol. All patients underwent basal PET (PET0) and interim PET (PET2) after 2 courses of ABVD. Scan results were determinate as positive or negative visually by consensus of 6 independent nuclear physician experts, using international harmonized criteria (Juweid's criteria). Semi-quantitavive analysis was made with maximum standardized uptake value (SUVmax) normalized to body weight and injection dose. SUVmax was measured on the most intense uptake area both on PET0 and on PET2. *Results.* 24 patients had a qualitative PET2 positive (28.6%). Lesion SUVmax averaged 10.3±4.4 g/mL on PET0, and 2.22±1.56 g/mL on PET2. At PET2, it was significantly higher in PET2 positive patients than in PET2 negative (3.7±2 g/mL versus 1.6±0.5 g/mL, L<0.0001), with a best SUVmax threshold equal to1.9g/mL on ROC curves (sensitivity 90%, specificity 82.1%). Considering the reference background, SUVmax was 1.84±0.5 g/mL in mediastinum (61% cases), and 1.4±0.5 g/mL in the surrounding background. The delta SUVmax was significantly lower in PET2 positive patients than in PET2 negative (66.6±21.2%, versus 79.6±12.8%, P=0.003), with an optimal threshold ≤77%. *Conclusions.* We described lower threshold SUVmax with semi-quantitative analysis to separate positive and negative PET2, than others studies using different visual criteria. Our results suggest that the harmonized criteria defined for end treatment PET reporting criteria can induce an excess of positive reports for interim PET in early stage cHL.

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POSITIVE INTERIM PET AFTER 2 ABVD IS MORE FREQUENT IN PATIENTS WITH UNFAVOURABLE STAGE I/II HODGKIN LYMPHOMA AND BULKY MEDIASTINUM THAN IN NON-BULKY.THE EORTC-GELA-IIL H10 TRIAL EXPERIENCE. THE EORTC-GELA-IIL H10 TRIAL EXPERIENCE

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Objective. To determine the percentage of interim PET$^+$ after two cycles of ABVD in patients with bulky mediastinum included in the EORTC/GELA/IIL H10 trial. *Material and methods.* From 557 patients with HL stage I or II classified unfavourable on the basis of either CSII ≥4 nodal areas or age ≥50 yrs or MT ratio ≥0.35 or ESR ≥50 (without B-symptoms) or ESR ≥30 (with B-symptoms) included in the H10 trial, we selected 224 patients: all had a PET/CT at baseline and after two ABVD. According to the MT ratio two groups were identified: Group I (bulky mediastinum) MT≥0.35, n= 100; Group II (non bulky) MT<0.35, n=124. The percentage of patients with B symptoms was similar in the two groups. PET/CT was reported using customized IHP criteria with an online centralized reading system averaging the opinions of 6 experts plus the including centre. The results were also compared with the five-point scale criteria. *Results.* The percentage of interim positive PET was significantly higher in Group I than in Group II (37% versus 19%, P=0.0051) when IHP criteria were used for PET reporting. The interobserver variability was significantly higher in Group I than in Group II: = 0.53 (95% CI, 0.39-0.69) and =0.67 (95% CI, 0.53-0.82), P<0.008. The percentage of interim positive PET observed in Group I was significantly lower when using the 5 point scale criteria with a liver cut-off as a reference background (22% versus 37%, P<0.01). However it was still significantly higher than the positive rate observed in group II (22% versus 9%, P=0.009). Moreover, this high positive rate increases with the M/T value, reaching when M/T>0.5 a similar value of 48% using IHP or five point scale. *Conclusions.* Patients with unfavourable Hodgkin lymphoma and bulky mediastinum have a significantly higher percentage of positive interim PET scans after two ABVD cycles than non-bulky patients. This difference is maintained whatever the criteria used for PET reporting and increases with the M/T ratio. The different characteristics between interim positive and interim negative patients in the bulky group are under investigation.

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PET/CT FINDINGS IN PATIENTS WITH HODGKIN'S LYMPHOMA (HL) AFTER ABVD COMBINATION CHEMOTHERAPY: PROGNOSTIC SIGNIFICANCE AND IMPLICATIONS FOR FURTHER RADIOTHERAPY AND FOLLOW-UP STRATEGIES

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Background. Mid-chemotherapy (CHT) and post-CHT PET results highly affect prognosis in HL. The predictive value of post-CHT PET findings in patients scheduled to receive additional radiotherapy (RT) is not clearly established. *Aims.* To retrospectively analyze PET/CT findings after the end of ABVD and determine their impact on the risk of progression using a treatment policy including complementary RT in stage I/II pts and selected pts with advanced disease. *Methods.* Between Dec 2004 and 2009, 221 pts [median age 30 years, 58% males, 98% classical HL, 27% B-symptoms, 30% clinical stage (CS) III/IV, median follow-up 21 months from PET] were treated with 4-8 cycles of ABVD: 167 pts with CR/CRu/PR underwent PET/CT after ABVD, 36 were not evaluated by PET/CT, 2 died early and 16 experienced rapid progression prior to PET/CT. RESULTS: PET/CT was negative in 130/167 pts (78%) and positive in 37 (22%). The 3-year progression free survival (PFS) was 92% for PET(-) and 41% for PET(+) pts (P<0.0001). For CSI/II pts 3-year PFS was 95% vs. 46% (P<0.0001), while for CSIII/IV pts 83% vs. 29% (P=0.006). Among PET(-) pts, relapse occurred in 3/92 CSI/II (89/92 irradiated; median 2930cGy) and 4/38 CSIII/IV pts (1/38 irradiated). Relapse was detected by clinical examination only in 4/7 pts. CSIII/IV was an adverse predictor of PFS among PET(-) pts (P=0.02). Among 37 PET(+) pts, 33 received RT (median 3800cGy); 11 pts had documented conversion to PET(-) after RT; only 2/11 relapsed (median observation 17 months from initial PET-Scan). *Conclusions.* Pts with positive PET/CT were in highly increased risk of progression despite additional RT. However, some pts converted to PET(-) after RT and might enjoy a more prolonged PFS. Longer follow-up is needed to accurately assess the positive predictive value of PET/CT after ABVD and the potential modulatory effect of RT. A negative PET/CT after ABVD was associated with excellent outcome within the initial years of observation for CSI/II pts, but less satisfactory outcome in more advanced disease (although RT was omitted in advanced disease). Thus, PET(-) advanced stage pts still require frequent follow-up, while frequent imaging procedures might be avoided in early stage pts.

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INVOLVED LEVEL – A POSSIBLE OF 3-D BASED TARGET VOLUME CONCEPTS FOR PEDIATRIC HODGKIN LYMPHOMA

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Purpose/Objective. The current radiotherapy target volume in pediatric Hodgkin lymphoma (PHL), reduced involved field (RIF), encompasses the extension of the primary involved lymph nodes at time of diagnosis adapted to the post-chemotherapy anatomy and topography. In a multi-center study, such as EuroNet-PHL study, this target volume definition might be not always suitable. The identification of the primary involved lymph nodes can be challenging on the post-chemotherapy planning CT scan. Target delineation might be biased because of morphological and

anatomic-topographic changes during CHT as well as different patient positioning for diagnostic and planning CT scans. To avoid misinterpretation of post-chemotherapy or subclinical nodal target volume in solid tumors, 3D-based lymph node levels, which are related to anatomical landmarks were implemented by V. Gregoire and O. Chapet. The boundaries of the levels are exact 3D-based defined and are independent from patient positioning. The levels include lymphatic tissue and exclude normal tissue like bones, muscles and vessels. In this study we question, if delineating a 3D-based level containing the primary involved lymph nodes is suitable for target delineation in PHL. Aim was to identify 3D-based delineation guidelines of primary involved lymph node levels (IL) and evaluate the feasibility and practicability for target definition in pediatric Hodgkin lymphoma (PHL) in comparison to RIF. *Material/Methods.* A review of the literature in respect of 3D-based guidelines for supradiaphragmatic lymph node delineation in radiotherapy for was performed. Guidelines for neck and for mediastinal node delineation were chosen. 17 patients with PHL Stage II with supradiaphragmatic involvement were delineated according to IL by three radiation-oncologists with experience in PHL. The primarily involved levels were defined on CT at time of diagnosis and delineated on post-chemotherapy planning-CT. The results were compared to RIF. *Results.* All three radiation-oncologists agreed that IL target definition is feasible and does not require more time. *Conclusion.* Anatomical based IL seems to be possible in PHL. Nevertheless IL has to be approved within a larger group of radiation oncologists before implementing in a multi-center study. Furthermore an atlas for IL concept might be helpful.

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3-D AND 4-D BASED TARGET VOLUME DEFINITION IN PAEDIATRIC HODGKIN LYMPHOMA (PHL)

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Purpose/Objective. Target volume (TV) concepts for PHL developed from "extended field" to "reduced involved field" (RIF) in the ongoing EuroNet-PHL-C1 study. RIF encompasses the extend of primary involved, PET positive, nodes at time of diagnosis adapted to topography after two cycles of chemotherapy (CHT). Due to excellent response to CHT TV definition might vary between different radiation oncologists. Adoption of TV concept based on 3D anatomical levels could result in more homogeneous target delineation in a multi-center trial. In our study we compare RIF on the one hand to 4D TVs defined by morphological changes or metabolic changes after two cycles of CHT and on the other hand 3D "involved node" (IN) to "involved level" (IL) for each 4D TV concept. *Material/Methods.* CTVRIF and 4D morphologic CTVCT-IN and metabolic CTVPET-IN (CT pos./PET pos. nodes after two cycles of CHT) and the associated anatomical levels CTVRIF-IL, CTVCT-IL, CTVPET-IL, were contoured for 17 PHL patients. Automatically generated PTV margins for CTVRIF, CTVCT-IN and CTVPET-IN were 1.5cm and reduced to 0.8 cm towards OARs. Regarding IL, the PTV margin was 0.5 cm for neck and 1.0 cm for all other sites. The different CTV and PTV volume were compared to the traditionally RIF volume. *Results.* Median CTVRIF was larger than CTVRIF-IL ($P<0.05$). Median CTVPET-IL was larger than CTVPET-IN ($P<0.05$). No significant difference between median CTVCT-IN and CTVCT-IL was observed. Regarding PTVs only the difference between median PTVRIF and PTVRIF-IL was significant. For both concepts, IN and IL, CT- and PET-based 4D CTVs decresed in volume compared to classical CTVRIF by almost 50% (CTVCT-IN, CTVCT-IL) up to 14% (CTVPET-IN) and 28% (CTVPET-IL). PTVs showed, as expected, the same trend. *Conclusion.* Although IL CTVs are slightly larger compared to IN CTVs, 3D based IL target definition is feasible and might lead to better quality in target definition. The practicability of IL target definition will be evaluated in a multi-center pilot study. The 4D volumes are smaller compared to RIF, the clinical feasibility of this concept has to be evaluated based on the experience of pattern of relapses after radiotherapy form previous studies.

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SINGLE INSTITUTION EXPERIENCE WITH INTERIM PET EVALUATION IN NEWLY DIAGNOSED CHL RECEIVING ABVD CHEMOTHERAPY: NEED FOR STANDARDIZATION

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Identification of patients with classical Hodgkin lymphoma (cHL) who are at risk for relapse after first-line therapy remains under intense research. Recently, Hutchings *et al.* used interim PET scan after 2-3 cycles of ABVD chemotherapy to identify patients who are at high risk for disease progression. Patients with interim PET negative status had 5 year progression free survival (PFS) of 91.5% compared with 38.5% for those whose PET were positive. Furthermore, when the analysis was restricted to patients with stage III-IV disease, the PFS at 2 years was 0% for PET positive and 78% for PET negative. In view of these results, we retrospectively reviewed data for 57 consecutive patients with newly diagnosed cHL treated at our institution and underwent a PET evaluation at baseline and after 2-3 cycles of ABVD. Initially we analyzed the data based on the clinical reports that were performed by 17 nuclear medicine radiologists prospectively before knowing treatment outcome. Using similar criteria reported by Hutchings *et al.*, 5 year EFS for PET negative patients was 75% and for PET positive was 54%. When the analysis was restricted to patients with stage III and IV (n=41), 5 year EFS was 74% for PET positive and 53% for PET negative. Interim PET was also reviewed retrospectively by two nuclear medicine radiologists using the 5 point scoring system (Barrington *et al.*, Blood, 2005). A score of 1-3 was considered negative and a score of 4-5 positive. One radiologist's reading demonstrated a 5 year EFS of 74% for PET negative and 50% for PET positive. When restricted to stage III-IV, 5 year EFS for PET negative was 75% and 33% for PET positive. The second radiologist's reading demonstrated an overall 5 year EFS for PET negative of 72% and 71% when restricted to stage III-IV. The interpretation of PET status varied between radiologists with 26/57 (46%) assigned different scores and change in status of 5/57 (9%). Our data confirms that interim PET status may predict treatment outcome in patients with cHL and support the need for standardization of interim PET reading criteria before adopting it to guide therapy.

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HDAC-BASED THERAPY FOR RELAPSED/REFRACTORY CHL: MDACC EXPERIENCE

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There is a strong unmet medical need for development of new therapies for relapsed and refractory classical Hodgkin lymphoma (cHL). Recently HDAC (histone deactylase) inhibitors have been identified as promising novel drugs for the treatment of cancer, including lymphoma. HDACs are critical for regulating cell proliferation, survival, angiogenesis and immunity and have shown to decrease the expression and secretion of cytokines and chemokines, including TARC. Here we report our experience at MD Anderson Cancer Center using a variety of HDAC inhibitors (HDACi) in patients with relapsed HL, including single agent trials and combination therapies. Initially we evaluated mocetinostat (MGCD0103) in a phase II trial with an overall response rate of 38% (n=23; 2 CR and 6 PR) in the 100 mg cohort (Bociek *et al.*, ASCO Meeting Abstracts, 2008). The dose was lowered to 85 mg, due to poor tolerability at 100 mg, which continued to show activity with 1 reported PR (n=10) and 2 patients with significant disease reduction. The recent multicenter phase II trial using panobinostat (LBH589) confirmed single agent HDAC activity in relapsed cHL post autologous transplant reporting a 26% ORR with the majority of patients experiencing tumor reduction (Sureda *et al.*, ASCO Meeting Abstracts, 2010). Entinostat (SNDX-275), given once every 2 weeks, is currently being evaluated in an ongoing phase II trial. Based on single agent activity, it was hypothesized that combining these agents with other novel therapies or with conventional therapies might synergize the activity translating into higher efficacy. The first combination administered azacitidine daily for five days followed by three times a week oral dose of mocetinostat at 85 mg. Response and tolerability data is forthcoming. An ongoing combination phase I/II trial combines HDACi panobinostat administered three times weekly and oral daily mTOR inhibitor everolimus. Finally, a randomized phase II study comparing ICE versus

panobinostat + ICE is evaluating whether the addition of panobinostat to ICE will improve CR rates prior to ASCT. In conclusion, pan and isotype selective HDACis have demonstrated promising single agent activity in the treatment of patients with relapsed cHL, with combination regimens currently being evaluated.

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RACE SIGNIFICANTLY INFLUENCES INCIDENCE PATTERNS AND PREDICTS MORTALITY: ADULT HODGKIN LYMPHOMA (HL) IN THE UNITED STATES (US)

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Background. Pediatric HL studies have suggested survival differences based on race. We examine herein the effects of race, age, and gender on incidence patterns and mortality among adults with HL in the US. *Methods.* We evaluated data for 13 SEER areas, several of which contain large Hispanic and Black populations. Case information was obtained from the 11/2009 SEER data submission released in 4/2010. We analyzed incidence, HL histology, and mortality rates according to race, age, and gender. We also examined incidence patterns across different decades. All analyses used SEER*Stat. *Results.* A total of 16,783 HL cases were diagnosed among residents in the 13 SEER registry areas during 1992-2007, with non-Hispanic Whites contributing the largest number (n=11,890), followed by Hispanics (n=2,190) and Blacks (n=1,724). Overall, Whites show a continued bimodal age-incidence curve (6.0/100,000 ages 25-29, 2.5/100,000 ages 50-54, and 4.5/100,000 age 75-79), while Blacks have a much less clear bimodal pattern (4.5/100,000 ages 25-29, 2.6/100,000 ages 50-54, and 3.0/100,000 ages 75-79). Further, Hispanics are distinctly not bimodal with a small increase at 20-24 (2.4/100,000) followed by an exponential-like increase with peak incidence at ages 80-84 (7.0/100,000).

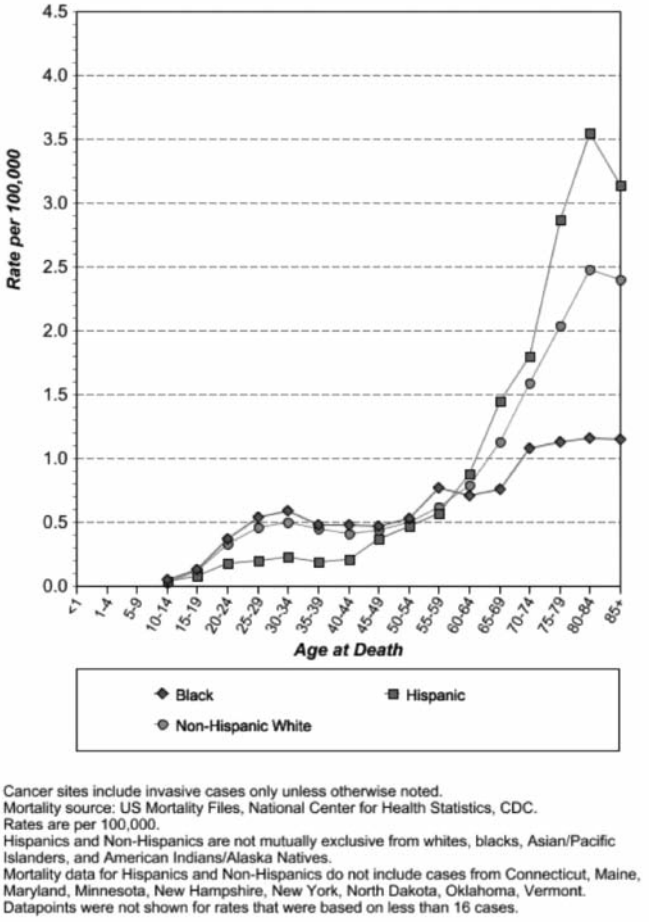

Figure 1. Age-specific (Crude) U.S. mortality rates by race/ethnicity Hodgkin Lymphoma, all ages, both sexes 1992-2006.

Moreover, HL is significantly more common in Hispanics than Whites in ages >65 years (4.7-7.0/100,000 vs 3.9-4.5/100,000, respectively, P<0.05). With gender, HL is more common in males than females, regardless of race. Interestingly, the male excess, however, does not occur until ages 30-34 (all races). Additionally, from 1975-2007, HL incidence increased in Black females (annual percent change (APC)=2.5; P<0.05) and White females (APC=0.4; P<0.05). According to histology, both nodular sclerosis and mixed cellularity are more common in Whites followed by Blacks and Hispanics, while in ages 60-84, both are significantly more common in Hispanics compared with Whites/Blacks. Over the past 20 years, mortality has declined within each race by 10.3-13.7% (P<0.05). However, age-specific ethnic survival disparities are apparent. For ages 65-84, Hispanics have a significantly increased mortality rate compared with Whites or Blacks (P<0.05). Conversely, among ages 20-44, Hispanics have the lowest mortality rate of all races (Figure 1). *Conclusions.* Multiple important epidemiologic and mortality differences are evident across and within races in adult HL.

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SURVEILLANCE CT IMAGING AND THE DETECTION OF RELAPSE IN HODGKIN LYMPHOMA

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Purpose. Patients with Hodgkin Lymphoma (HL) routinely undergo surveillance CT imaging for up to 5 years following completion of therapy (Rx). Current protocols require between 5 and 11 surveillance CT scans, resulting in considerable additional radiation exposure, without clear benefit. The objective of this study was to determine the contribution of surveillance CT, as compared to clinical symptoms, laboratory and physical exam (PE) findings, to the detection of disease relapse. *Materials and Methods.* 216 pts, age ≤22 years old, with intermediate (N=53) and advanced stage (N=163) HL were treated on multi-center trial POG 9425. Pts received 3 or 5 cycles of chemotherapy (ABVE-PC) and radiation therapy. CTs were obtained at 0, 6, 12, 24 and 30 months post treatment. Data from pts who relapsed were retrospectively reviewed to determine whether imaging or symptoms/PE findings identified disease relapse. Correlation was made with time to relapse, disease stage and site of relapse. *Results.* After >8 yrs of follow-up, 23/216 patients experienced relapse (10.6%). Median time to relapse was 7 months (range: 0-49 months). 21/23 relapses were local. Relapses occurred in both intermediate (5/23) and advanced stage (18/23) disease. 14/23 pts had disease detected based on clinical symptoms, lab or PE findings. 4 pts had disease detected by imaging within the first year post-Rx; 1 pt had imaging done for unrelated reasons. Only 4 pts, all of whom relapsed >1 year post therapy, were asymptomatic and had disease detected solely on the basis of surveillance imaging. *Conclusions.* Pts with HL have an excellent (>85%) 5 year EFS. Risk of relapse is greatest within the first year off Rx. In this study 14/23 relapses occurred ≤12 months after completing treatment. Routine surveillance imaging after the first year detected relapse in only 4 pts who did not have new clinical findings. ~400 scans were mandated by protocol requirement to detect these 4 events. These data suggest that CT may be over-utilized in routine post-treatment surveillance of pts with HL and modifications are indicated for protocols requiring long-term routine surveillance CT.

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THE NEWLY DEVELOPED PVAG-REGIMEN IS ACTIVE AND FEASIBLE IN ELDERLY PATIENTS WITH INTERMEDIATE OR ADVANCED STAGE HODGKIN LYMPHOMA: RESULTS OF A PHASE II STUDY OF THE GERMAN HODGKIN STUDY GROUP (GHSG)

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About 20% of all patients diagnosed with Hodgkin Lymphoma (HL)

are older than 60 years. They have a poor prognosis, mainly due to an increased toxicity of chemo- and radiotherapy resulting in a higher treatment-related mortality and insufficient dosing of the applied treatment. In order to improve tolerability, the PVAG regimen (prednisone, vinblastine, doxorubicin, and gemcitabine) was developed. Here we report on the final analysis of this multi-center phase II study for elderly HL patients. 61 patients were recruited; treatment consisted of 6 cycles PVAG in patients achieving a CR after 4 cycles or 8 cycles in case of PR after 4 cycles. Patients who did not achieve CR after chemotherapy received additional radiotherapy. Primary endpoints were administration of adequate dose without delays and response rate 3 months after treatment. Secondary endpoints included WHO grade III/IV toxicities, and occurrence of early progression. 59 patients (median age: 68 years) were evaluated, of which 59% were male and 93% had advanced stage disease. The relative dose intensity (relative dose divided by relative chemotherapy duration) was at least 80% in 45 patients (76%). 88% of all cycles started without delay (max. 1 day) and the mean relative dose of all agents was slightly decreasing over time but always exceeded 90%. WHO grade III/IV toxicities were documented in 43 patients (75%). Only 3 patients terminated CT because of excessive toxicity. 11 Patients (19%) received consolidating radiotherapy. In total, 46 patients responded with CR/CRu (78%), 2 with PR (3%), 2 with no change (3%) and 4 with PD (7%); in 2 patients, the outcome was unknown and 3 patients died before restaging. 15 progressions or relapses and 17 deaths have been observed, of which only 1 was due to PVAG related toxicity but 8 were due to HL (median observation time: 30 months). The 2-year-estimates for OS and PFS were 82% (95%-CI 68% to 90%) and 65% (95%-CI 50% to 76%), respectively.In conclusion PVAG is safe and feasible in Hodgkin patients older than 60, further research is warranted to determine the efficacy.

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ANALYSIS OF CENTRE EFFECTS ON PROGRESSION FREE SURVIVAL FOR HODGKIN-LYMPHOMA PATIENTS WITHIN THE GERMAN HODGKIN STUDY GROUP

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Introduction. Clinical trials in Hodgkin lymphoma (HL) patients have improved the outcome remarkably during the last decades. However, new regulatory rules make multicentre investigator-initiated-trials highly complex and expensive. Since it had been speculated that treatment in smaller centres might be associated with a poorer outcome, this hypothesis was analysed using the GHSG-database. *Methods.* Between 1988 and 2002, 9.150 patients were randomised in the GHSG-trials HD4-12. To test the hypothesis, we considered 2.223 patients randomised 1988-1998 (HD4-9). We defined "small" (<50 patients) and "big" centres (≥50 patients). In the multivariate model, the patient number per centre was used as a continuous variable. Progression free survival (PFS) was analysed using Kaplan-Meier and log-rank test. The Cox regression analysis included 2.221 patients and 532 events. For hypothesis validation, different datasets were analysed: 2.216 patients (512 PFS-events) from HD4-9, and 3.682 patients (509 PFS-events) from HD10-12. *Results.* In Germany, clinicians from 52 university hospitals (UH), 304 general hospitals (GH) and 144 independent outpatient clinics (IOC), randomised 8.121 patients in the GHSG-trials. 42% of patients came from UH, 47% from GH and 11% from IOC. The median number of randomised patients was 103 in UH, 33 in GH and 12 in IOC. Patients from small centres were older, had more often early stage and a diagnosis in the later studies (HD7-9) than patients from big centres. The 5-year PFS-rate is 79% (95%-CI=[76-81]) for each group and no statistical difference in PFS was observed. According to Cox-regression, following parameters were significantly (P<0.01) associated with poor PFS: male sex, older age, B-symptoms, advanced stage, earlier study generation, only radiotherapy and no BEACOPP arms. No independent contribution of the randomising centre size for PFS could be found (HR=1.00, 95%-CI=[0.99-1.00]). No correlation between the type of centre (UH, GH or IOC) and PFS could be found. These findings were confirmed in the validation-cohorts. *Conclusion.* The analysis did not show any correlation neither between PFS and centre size nor between PFS and type of centre. As this analysis was very well powered, randomising centre effects on the outcome of HL patients within the GHSG can be excluded.