Hodgkin's lymphoma

151 IS THE NATURAL HISTORY OF HODGKIN LYMPHOMA (HL) CHANGING?

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Introduction: Age specific incidence (ASI, here expressed as cases per 100 000 population), for HL characteristically shows a bimodal distribution with a 3rd decade peak, 5th decade trough and gradual rise in numbers with increasing age. This reported pattern is similar for both sexes, with a relative excess of males at all ages.

Methods: We conducted consecutive audits in the South West of England, encompassing 22 hospitals, for the years 1993 (96 cases), 1999 (93) and 2005 (148), to examine the patient diagnostic and treatment pathways and long term outcomes. These unselected cohorts included all HL known to the diagnosing hospital. The number of participating units varied between the three audits and an accurate estimate of the underlying population and ASI of HL was not possible from the data obtained. Complete SWPHO cancer registry data for the same periods were therefore examined.

Results: The crude age distribution of the 1993 and 1999 cohorts was similar and in line with the recognised bimodal distribution. However, the 2005 cohort showed a distinct departure from this pattern, with a relative excess of male cases in the 5th decade and an absolute increase in male cases overall. The 1999 cohort had shown a less marked excess for males compared to 1993. Complete cancer registry data confirmed a similar shifted age distribution for males in the 5th decade: 1993: 2.47 (1.06-4.86) 1999: 2.21 (0.89-4.56) 2005: 6.38 (3.95-9.76). This unexplained change was not seen for females and the relative ASI remained stable for both sexes for other ages except for the 8th and 9th decades where increases were likely to be due to case ascertainment.

Conclusions: 1) Regional audit uncovered a possible change in the recognised pattern of ASI for HL in males. This is unlikely otherwise to have been recognised. 2) The change in ASI for males may represent a true shift in the natural history of HL and needs further examination. 3) If confirmed, such a change in HL demographics would have implications for disease aetiology, health service planning and treatment strategies.

152 U-HO1, A NEW CELL LINE DERIVED FROM A PRIMARY REFRACTORY CLASSICAL HODGKIN LYMPHOMA

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Introduction: Although Hodgkin lymphoma (HL) is not a rare disease and the occurence of HL in young patients point to a genetically determined risk factor, its molecular oncogenesis is largely unknown and less than 10 HL cell lines exist worldwide. Here we describe a novel permanent human HL cell line, U-HO1, derived from the end stage of refractory nodular sclerosing classical HL of a male patient.

Results: Since its establishment in 2005, U-HO1 has maintained stable characteristics *in vitro* and has a doubling time of about 4 days under standard culture conditions. U-HO1 forms typical Reed/Sternberg cells in suspension, is EBV negative, lacks HLA-ABC- but expresses HLA-D- proteins/CD74 and surface exposes CD15 together with CD30 in the absence of CD19 and CD20. Karyotype analysis of U-HO1 revealed a hyperdiploid karyotype with multiple clonal aberrations.

Most significant is an elongated chromosome 2, der(2)t(2;10)(q35;q16.1)add(2)(p13). CGH analysis revealed the following imbalances: ish cgh dim(1)(p13p31)(p12q21), enh(2)(p13p23), dim(4)(q31.3qter), enh(6)(q22q27), enh(12), enh(18),enh(20)(q13.1pter). FISH analysis showed about six-fold amplification of *REL* and *BCL-11A*. U-HO1 shows strong nucclear staining of cRel indicating an activated NF-kB pathway that enhances growth activity and protects Hodgkin cells from apoptotic cell death. Thus, U-HO1 is prototypical for classical HL in every aspect tested so far. As an outstanding feature compared to the existing HL cell lines, U-HO1 has high levels of microRNA transcripts of *MIRN216* and *MIRN217* located in the amplicon 2p16. Among the targets of hsa-miR-216 are the mRNAs of *JAK2, BCL11B, RAB6A, -6C, -10, -11A*, and *LAMC1*, among those for hsa-miR-217 are the mRNAs of *BCL11A, BCL2*, and *BCL2L13* (for more details e.g. http://pictar.bio.nyu.edu/).

Conclusions: These preliminary results render U-HO1 an interesting new HL cell line that hopefully will foster future research in Hodgkin's disease.

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153 - WITHDRAWN

154 DEPLETION OF GLUTATHIONE ENHANCES ARSENIC TRIOXIDE (AS_2O_3)-INDUCED APOPTOSIS THROUGH MITOGEN ACTIVATED PROTEIN KINASE (MAPK) PATHWAYS IN HODGKIN LYMPHOMA (HL) AND NON-HODGKIN LYMPHOMA (NHL) CELLS

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Background: We determined the mechanism of cytotoxicity of As_2O_3 alone and in combination buthionine sulfoximine (BSO) in HL and NHL cell lines.

Methods: Ramos, HF-1, and SUDHL4 (NHL), and L428 (HL) cells were cultured with increasing As_2O_3 concentrations (1.0μm-10μm) at 24-72 hours with/without the oxidizing agent, BSO (100μm), and with/without caspase inhibitors. Apoptosis was measured by annexin-V/propidium iodide (Ann+/PI+) and detected by flow cytometry (FACS). Reactive oxygen species (ROS) were measured by oxidation of 2′7′dichlorofluorescein diacetate (H_2DCFDA) to DCF and analyzed by FACS. Immunoblots were performed for bcl-2, PARP, cleaved caspases and MAPK pathways (ERK, JNK, and p38).

Results: As_2O_3 alone resulted in dose and time dependent apoptosis in all cell lines (HL and NHL) with >75% Ann+/PI+ at 48-72 hours. In Ramos and L428 cells, a combination of As_2O_3 (2μM) and BSO 100μM was synergistic resulting in >80% Ann+/PI+, while either agent alone resulted in <15% apoptosis (p=0.001). A 4-fold increase in ROS was seen in all cell lines with As_2O_3/BSO. Both ROS and apoptosis induced by As_2O_3/BSO were reversible with the anti-oxidant N-acetylcysteine (NAC) (10mM). Furthermore, As_2O_3 induced PARP and caspase-3 cleavage in all NHL cell lines, but not L428. In Ramos, Z-VAD-FMK and Z-IETD-FMK blocked As_2O_3 induced apoptosis (suggesting a caspase-dependent mechanism), but had no effect on As_2O_3/BSO-induced cell death (caspase-independent). We found up-regulation of p-p38 in Ramos cells, while in L428, p-ERK was activated with As_2O_3/BSO and As_2O_3. Inhibitors of MEK1/2 and JNK enhanced As_2O_3 induced apoptosis in Ramos.

Conclusion: As_2O_3 alone induced dose- and time-dependent apoptosis in HL and NHL cells, which was significantly enhanced with the addition of BSO. Furthermore, As_2O_3/BSO-related apoptosis was ROS dependent. As_2O_3 alone resulted in caspase-dependent apoptosis, while addition of BSO resulted in caspase-independent apoptosis. In addition, As_2O_3 with/without BSO resulted in activation of MAPK pathways. These data provide a basis and a mechanism for As_2O_3-induced cell death in HL and NHL and have therapeutic implications.

155 ABERRANT EXPRESSION OF THE TH2 CYTOKINE IL-21 IN HODGKIN LYMPHOMA CELLS REGULATES STAT3 SIGNALING AND ATTRACTS TREG CELLS VIA REGULATION OF MIP-3α

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Introduction: The malignant Hodgkin-/Reed-Sternberg (HRS) cells of Hodgkin lymphoma (HL) are derived from mature B cells, but have lost the B cell-specific gene expression pattern. Consequences of such a lineage infidelity for lymphoma pathogenesis are currently not defined. Here, we report in HRS cells an aberrant expression and activity of the common cytokine-receptor γ-chain (γc) cytokine IL-21, which is usually restricted to a subset of CD4+ T cells.

Material and Methods: Experiments were performed using a panel of HRS and non-Hodgkin cell lines. The analysis of IL-21 and MIP-3α expression and activity was performed by use of RT-PCR, Western blot and FACS analysis, ELISA, treatment with rhIL-21, specific inhibition of IL-21 signaling, and migration assays with freshly isolated PMNC. Apoptosis was analyzed by Annexin V/PI staining. Primary HL cases were analyzed for expression of MIP3α and IL-21 by IHC.

Results: IL-21 activates STAT3 in HRS cells, up-regulates STAT3 target genes, and protects HRS cells from CD95 death receptor-induced apoptosis. Furthermore, IL-21 is involved in up-regulation of the CC chemokine MIP-3α in HRS cells which in turn attracts regulatory T cells towards HRS cells. IHC analyses confirmed expression of IL-21 and MIP-3α in HRS cells in 9 out of 10 HL cases analyzed, independent of the EBV status.

Discussion: Together, we describe for the first time the endogenous production of IL-21 by human malignant cells. IL-21 exerts direct effects on HRS cells and influences the composition of the cellular infiltration surrounding HRS cells. Thus, inhibition of IL-21, but also MIP-3α might provide a new treatment strategy for HL which would not only directly target HRS cells but might also enforce a HL-directed immune attack.

156 COMBINATION OF GENE PROFILING AND TISSUE MICROARRAY ANALYSIS IDENTIFIES THE B-CELL/ PLASMACYTOID DENDRITIC CELL–SPECIFIC GENE BCL11A AS A ROUTINE MARKER OF FAVOURABLE OUTCOME IN CLASSICAL HODGKIN LYMPHOMA

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Background: After treatment for classical Hodgkin lymphoma (cHL), about 40% of patients present either refractory disease or relapse. Identification of patients who would require more intensive therapy is thus a crucial challenge.

Methods: A training set of 63 cHL frozen tissue samples was profiled using Affymetrix microarrays. A validation set of paraffin tissue samples from 154 cHL patients (median follow-up of 75.7 months) was analysed using immunohistochemistry (IHC) on tissue microrrays.

Results: Using a supervised analysis, the signature of EBV+ vs EBV- HL tissues was enriched in genes characteristic of Th1 and antiviral responses including IFNG. 38 genes were significantly overexpressed in HL patients with complete remission, when compared to those with refractory disease or relapse. They were involved in the function of B-cells and plasmacytoid dendritic cells (pDCs), like BCL11A. IHC validation using both univariate and multivariate Cox models confirmed that high numbers of BCL11A+ reactive cells were correlated with both overall survival and event free survival ($p < 0.01$). Univariate Cox model showed asignificant correlation between outcome and the IHC expression of FOXP-3, TIA-1 and CD20. No prognosis value was found for IHC detection of BCL2, LMP-1, PD-1, CD57, tryptase, granzyme-B, PS100, CD8, STAT1 and CD123.

Conclusions: Identification of BCL11A as a powerful routine IHC prognosis marker might help to select cHL patients who would benefit from reduced therapy to avoid late toxicity. This also suggests that innate immunity, including pDCs, play an important role in the defence against cHL tumor cells. Thus, stimulation of pDC activity and intra-tumoral Th1 responses against EBV may be a basis for novel treatment strategies.

157 MECHANISMS OF DEPSIPEPTIDE INDUCED CELL DEATH IN REED-STERNBERG CELLS

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Background: It was speculated that simultaneous inhibition of multiple signaling pathways might be a promising strategy to target HL. In the present study we tested the effect of histone deacetylase (HDAC) inhibition using depsipeptide (Gloucester Pharmaceuticals) in cHL cell lines in vitro.

Material and Methods: Molecular mechanisms of toxicity were analyzed in cHL cell lines (L1236, L428, L591, L540Cy) using viability and apoptosis asays with z-vad-fmk as a pan-caspase inhibitor. In addition, whole genome RNA expression analysis (Affymetrix Array 133 Plus2.0) and functional NFkB binding assays (TransAM) were performed.

Results: It is shown that depsipeptide is effective at submicromolar concentrations in all cell lines studies. It acts mainly by apoptosis induction as shown by caspase viability assays, biochemical assays and FACS; upregulation of p21; and cell cycle inhibition in G2/M. It is also shown that HDAC induces upregulation of RelA/p65 binding activity.

Conclusion: Depsipeptide induced protein acetylation results in transcriptional changes of a large number of pathogenetically relevant genes, especially of apoptosis and cell-cycle related genes. It induced toxicity in all cell lines studied despite the striking finding of increased RelA/p65 binding activity in depsipeptide treated cells. Our preclinical data suggest that HDAC inhibition using depsipeptide might be a promising approach for the treatment of patients with HL.

158 SHIELD - STUDY OF HODGKIN LYMPHOMA IN THE ELDERLY/ LYMPHOMA DATA BASE: PROGRESS REPORT

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Introduction: Hodgkin lymphoma (HL) is a curable disease but outcome in patients >60 years has not improved. The SHIELD programme offers a phase II interventional study (VEPEMB: vinblastine, etoposide, prednisolone, procarbazine, endoxana, mitoxantrone, bleomycin) and a registration element for patients ineligible because of frailty /palliative approach or use of an alternative regimen.

Results: At January 2008 a total of 153 patients had been enrolled in the programme. 64/153 VEPEMB patients; age range 60-85 years, median age 72 years, Stage I and II 28/64 patients (receiving VEPEMB x 3 ± RT); 35/64 stage III and IV patients (receiving VEPEMB x 6 ± RT) and 1/64 patients not known. 30/64 completed full course of treatment, 15/64 required major dose reduction or discontinued therapy and 19/64 patients data pending. Histological types: 26/64 mixed cellularity; 27/64 nodular sclerosing; 7/64 unclassified; 4/64 lymphocyte rich. There were no treatment related deaths in the VEPEMB study but grade III/IV haematological toxicity was encountered in later courses requiring use of routine GCSF. Deaths on VEPEMB treated patients were 3/64 as a result of HL and 5/64 deaths not related to disease or treatment. Registration patients consisted of 89 patients including 57 from German Hodgkin Study Group, treated with BACOPP therapy (subject to separate analysis). The remaining 32 UK registration patients consisted of 12/32 stage I and II, 19/32 stage III and IV and 1/32 unknown. 13/32 patients were treated with ABVD; 11/32 were treated with CLVPP; 1/32 patient received PECC and 7/32 data pending. In this group there have been 9/32 deaths; 1 treatment related, 6 HL related and 2 HL unrelated.

Discussion: This on-line study programme has already prospectively accrued the largest number of HD elderly patients worldwide, and is set to double the number in a two year period. Such a study approach is applicable to other rare 'orphan' areas of lymphoma research. Web site www.shieldstudy.co.uk

159 IS ROUTINE BONE MARROW BIOPSY NECESSARY IN STAGING PATIENTS WITH HODGKIN DISEASE IN THE PET ERA?

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Introduction: Initial adequate staging of Hodgkin's lymphoma (HL) is mandatory for tailored treatment, including bone marrow biopsy (BMB). Whereas pretreatment PET(CT) is currently not formally mandatory, it has been strongly recommended to facilitate interpretation of equivocal post therapy PET/CT scans and provide useful information regarding delineation of involved field radiation therapy. The aim of this retrospective study was therefore to assess the place of BMB in initial staging of HL patients without bone or bone marrow involvement detected on PET/CT.

Patients and Methods: All data from 48 patients (36 male, 12 female, mean age 38) with newly diagnosed HL and who had both PET/CT and BMB before start of treatment were collected.

Results: 4/48 patients had lymphomatous involvement on BMB. All those 4 patients were also positive on PET/CT scan. In 9 additional patients, PET/CT scan showed multiple foci suggestive of bone/ bone marrow involvement. Further confirmation of these lesions was obtained by MRI in 3 patients and on prestating CT in 1. BMI findings on PET/CT led to upstaging of 6 patients with initial stage II or III; 3 others were already stage IV.

Conclusion: PET/CT appears better than BMB to detect bone/bone marrow involvement. We therefore conclude that, in patient with pre-treatment negative PET/CT, BMB is probably not justified.

160 RISK ADAPTED BEACOPP BASED ON EARLY INTERIM SCINTIGRAPHY CAN BE USED FOR REDUCTION OF CUMULATIVE DOSE OF CHEMOTHERAPY AND PRESERVATION OF FERTILITY IN PATIENTS WITH STANDARD AND HIGH RISK HODGKIN LYMPHOMA (HD)

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This prospective study evaluated outcome of HD pts whose therapy was tailored based on results of scans performed after 1 or 2 cycles of chemotherapy, thus reducing dose for early responders and maximizing the dose for late responders. The study was started in 1999 for pts with HD aged 18-65 ys. Eligibility criteria were unfavorable stages I, II and stage III or IV. Disease was defined according to the International Prognostic Score (IPS). Standard risk pts were treated with 2 cycles of standard BEACOPP (SB) and those with IPS ^{3} 3 got 2 cycles of escalated BEACOPP (EB). Baseline Ga^{67} or hybrid PET/CT scan was done at diagnosis and after the 1st or 2nd cycle for 58 and 66 pts, respectively. If early interim scan remained positive, additional 4 cycles of EB were used; otherwise SB was given. The data were previously reported (Blood, ASH 2005); herein is an update with longer follow-up and 16 added patients.124 pts aged 18-63 (median 31) are reported. CR rate was 97%, 5-y event-free (EFS) and overall survivals (OS) were 87% and 92%, respectively at a median follow-up of 55 m (5-95). 5-y EFS and OS were similar for standard and high risk pts. HD progressed in 3/12 pts with interim positive PET/CT versus 1/54 with negative PET ($p<0.02$). Negative predictive values of early normal PET and GA^{67} scans are 98% and 84%, respectively, $p<0.03$. One pt developed secondary leukemia after relapse and high-dose chemotherapy. One pt died from an unrelated cause. 37 females < 40 years old were assessed for fertility status: 14 conceived during follow-up and delivered 12 healthy babies, 1 is currently pregnant and 2 terminated their pregnancy. 17 other patients had cyclic ovarian function. 83% kept their ovarian function. Conclusion: PET/CT is useful for making an early interim decision about chemotherapy dose on an individual basis. The results of 6 cycles of risk-adapted BEACOPP compare favorably with the reported data following 8 cycles of EB.

161 FDG-PET FOR ASSESSMENT OF EARLY THERAPY RESPONSE AFTER 4 CYCLES OF CHEMOTHERAPY IN ADVANCED STAGE HODGKIN LYMPHOMA

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Introduction: The aim of this study is to assess predictive value of PET after four cycles of BEACOPP therapy of advanced stage of HL treated within HD15 study of GHSG.

Material and methods: Total of 50 pts were evaluated. Median follow – up of living pts is 22 months and median age 29 years. One patient PET4 negative died due to acute toxicity of treatment.

Results: 36/50 pts had negative and 14/50 pts (28%) had positive PET after four cycles of BEACOPP (PET4): 13/14 had initially a large mediastinal mass, IPS 3 – 6 six, 0 - 2 eight pts. After the completation of chemotherapy, nine patients had residual disease that was still PET positive (PET 6 or PET 8). Two of them with very large residual mediastinal massreceived successful salvage therapy with HDT and ASCT. All of the first – line postchemotherapy PET positive pts were irradiated. All living pts is in complete remission (CR or CRr) at the time of this report.

Conclusions: Fourteen out of fifty pts (28%) treated within HD15 study GHSG had positive PET scan after 4 cycles of the chemotherapy.Thirteenof these had initially a large mediastinal mass and two of them were treated by salvage therapy with HDT with ASCT, because of tumour inadequate response. In our analysis we have found that PET4 positive patients belong mostly to the group with initial large mediastinal mass. This finding supports again well known observation that the large mediastinal mass is the high risk factor and requires intensive type of treatment. However, considering still low number of patients and short follow–up, any definite conclusion regarding the prognostic impact of this finding is pending.

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162 10-YEAR RESULTS OF THE HD9 TRIAL OF THE GERMAN HODGKIN STUDY GROUP (GHSG) COMPARING BASELINE AND ESCALATED BEACOPP CHEMOTHERAPY FOR ADVANCED HODGKIN LYMPHOMA

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The HD9 trial compared two different doses (baseline and escalated) of the novel chemotherapy regimen BEACOPP in advanced Hodgkin lymphoma. The previous analysis with a median follow-up of 5 years showed improved tumor control and overall survival for $BEACOPP_{escalated}$. The present 10 year analysis in March 2007 aimed to update and confirm these results and to monitor late effects. Patients aged 16-65 years with untreated advanced Hodgkin lymphoma (stage IIB/IIIA and risk factors or stage IIIB/IV) were randomized to (A) 4 double cycles COPP/ABVD, (B) 8 cycles $BEACOPP_{baseline}$ or (C) 8 cycles escalated BEACOPP (doxorubicin, cyclophosphamide and etoposide at 140%, 192% and 200% of standard doses, respectively). The chemotherapy was followed by irradiation of initial bulky and residual disease for all treatment arms. Accrual of at least 900 patients was planned so as to detect a 9-10% improvement in the primary endpoint, freedom from treatment failure (FFTF). 1196 of 1201 eligible, randomized patients were evaluable (261, 469 and 466 in arms A, B and C, respectively). The median follow-up times were 122, 111 and 107 months in arms A, B and C, respectively (29-32 months longer than in 2004). Corresponding 10-year FFTF rates were 64%, 70% and 82% respectively ($p<0.0001$). FFTF was significantly better in the escalated BEACOPP arm than in the $BEACOPP_{baseline}$ arm ($p<0.0001$). 10-year overall survival rates were 75%, 80% and 86% respectively ($p<0.001$). Overall survival was also significantly better in the $BEACOPP_{escalated}$ arm than in the $BEACOPP_{baseline}$ arm ($p=0.0053$). The death rates for HL were 11.5%, 8.1% and 2.8% in arms A, B and C respectively. A total of 74 second malignancies were documented: 1, 7 and 14 acute myeloid leukemias (AML); 7, 8 and 5 non-Hodgkin lymphomas (NHL); 7, 16 and 9 solid tumors/others in arms A, B and C respectively. The corresponding overall secondary malignancy rates were 5.7%, 6.6% and 6.0%. After 10 years of follow-up dose escalation of BEACOPP chemotherapy results in a stabilized significant improvement in long-term FFTF and OS. The risk of secondary AML, although increased in this study after $BEACOPP_{escalated}$, amounts to 0.9% in the succeeding HD12 study with $BEACOPP_{escalated}$ in 1502 randomized patients and 4 years median follow-up.

163 MVPP IN HODGKIN LYMPHOMA AS INITIAL THERAPY AND 'APPROPRIATE' INTERVENTION AT FAILURE: LONG TERM FOLLOW-UP RESULTS

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The management of anatomically advanced Hodgkin's Disease (HD) was revolutionised by the introduction of cyclical combination chemotherapy. The alkylating agent based regimen 'MOPP' or its variants were 'best standard care' for a quarter of a century, beginning in the 1960s. Long follow up data from this era at a single centre utilising 'MVPP' as initial treatment and appropriate salvage if it failed, are presented below. From 1968-1992, 237 patients with newly diagnosed stage III-IV HD were treated with 'MVPP' as standard care, or in comparison with total nodal irradiation (stage IIIa only, 27) or other chemotherapy (62). Details (median years 35, range 14-79), Male/Female 172/65, stage IIIa 70, IIIb 64, IVa 27, IVb 76; histology: N/S 136, M/C 57, LP 2, LD 11, other 12. With a minimum follow up of 15 years only 4 patients having been lost between 2 and 6 years 106/237 (45%) are alive, free of Hodgkin's Disease for a minimum of 2 years, 88/237 (37%) in 1st, 17/237 (7%) in 2nd and 1 (1%) in 5th remission. 36 (15%) have developed 2nd malignancy,131 (55%) have died, 44 (19%) in remission, 30 (13%) in 1st remission, and 57 (24%) after one or more recurrence, causes of death being HD 66 (28%), 'therapy' 19 (8%), 2nd malignancy 18 (8%) (out of 36), cardiac failure 18 (8%), other 10 (4%). The likelihood of prolonged survival correlated with youth (.001), histology (N/S + M/C) (.001), and low stage (.04). MVPP as initial therapy, and 'appropriate' intervention at failure has resulted in 45% being alive, disease free and probably cured of HD, but 36 (15%) being dead prematurely without recurrence probably related to therapy. These results of therapy no longer frequently used serve as a yard stick against which to judge current strategy.

164 DOSE-DENSE/DOSE-INTENSE ABVD IN HIGH-RISK HODGKIN'S LYMPHOMA

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Background: An optimal definition of risk–adapted therapy for Hodgkin's lymphoma is still under discussion. In June 2004 we started a phase-2 study to explore the possibility to improve the performance of ABVD, creating 2 new variants called dose-dense ABVD, for intermediate-risk pts, and dose-dense/dose-intense ABVD (dd-di ABVD), for high-risk (HR) pts. Here we focus on data concerning the HR subset.

Materials and methods: Sixty pts were enrolled in the study. Thirty-seven out of 60 pts constituted the HR subset. HR features were: stage III (N=7), stage IV (N=19), stage II B with bulky and/or E-disease (N=11). Baseline characteristics of pts: M/F=12/25; Age>45-yr; N=6(16%); Bulky N=21(57%); E-disease N=21(57%); B-symtoms N=30(81%); ESR>50 N=17(46%); high-LDH N=15(41%); IPS ≥ 3 N=15(41%; N sites ≥ 4 N=24(65%). Strategy concepts of dd-di ABVD: (1) Each pt received a total of 6 cycles. (2) Adriamycin was escalated from 50 to 70 mg/m2 in cycles 1,2,3,4. (3) The inter-cycle period was shortened from 28 to 21 days for all 6 cycles; the 4 drugs were delivered at d 1 and 11 of each cycle. (4) G-CSF was given from d4 to d8 of each course. (5) Tx 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. (6) Radiotherapy was reserved only for bone lesions.

Results: The Planned-RDI of the schedule was 1.42. The median administered RDI was 1.36 (1.10-1.55). Thirty-four out of 37(92%) pts obtained the early CR. 2/37 pts were slow-responders: a 26-yr old girl (CS II_4XB) and a 51-yr old woman (CS IVEB); 1/37

pts, a 30-yr old man, with residual PET+ lesions at the end of the 4th cycle, was considered a failure. Finally, 36/37 (97%) pts were in CR. Two pts (5%) had a biopsy-proven relapse (<12-mo): a 29-yr old girl (CS IVXEB) and a 33-yr old man (CS IVEA). A 60–yr old man (CS IVEB) died of pneumonia 1-mo after the end of the last cycle. All the other pts are alive and free of disease. With a median follow-up of 20 (range 4-41) and 22 (6-43) months, the DFS and OS were 92% and 97% respectively; no significant differences were registered among stage-subsets. Hematologic toxicity was moderate and self-limiting, with grade 3 or 4 neutropenia and anemia occuring in less than 20% of courses. A limited number of G3-G4 events determined the need for intervention or hospitalisation.

Conclusions: dd-di-ABVD is feasible, well tolerated and highly active in newly diagnosed patients with HR HL.

165 HIGH-DOSE SEQUENTIAL CHEMOTHERAPY (HDS) FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IN RELAPSING/REFRACTORY HODGKIN LYMPHOMA (HL): LONG-TERM RESULTS

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Introduction: Starting from January 1986 235 patients (pts.) were enrolled in a multicenter clinical trial to explore the role of HDS followed by ASCT in refractory or relapsed HL.

Patients and methods: The mean age was 32.4 (11-61), limited (II) or advanced stage (III-IV) in 104 and 131 pts, respectively. The first-line chemotherapy consisted in ABVD in 126 pts., hybrid/alternating MOPP/ABVD in 57, or other in 52. Two or more lines of chemotherapy were given in 22 patients. HDS plus ASCT was given for resistant o relapsing disease in 63 and 172 pts. Pts. in first or second relapse or more were 143 and 19, respectively. The first relapse occurred < or > 1 year (e-Rel, 54 pts.; l-Rel, 88 pts.) after treatment end. HDS included DHAP, cyclophosphamide (7 gr./m^2), methotrexate (8 gr/m^2) or ARAC (4 gr/m^2 x 4 days), etoposide (2 gr/m^2). The conditioning regimen was BEAM (92), mitoxantrone and melphalan (114) or TBI (20).

Results: ASCT was done in all but 9 pts.: 4 for peripheral stem cell (PBSC) harvest failure and 5 for disease progression. The mean value of CD 34+ reinfused was 6.4 x10^6/kg PBSC (189 pts). and 5.3 x 10^6/Kg for BM transplants (21 pts), unknown in 16. After a median follow-up of 53.8 months (2-261) 139 pts. were alive and 96 had died. The causes of death were progressive disease (70), infections (5), renal/hepatic toxicity (4) dilatative myocardiopathy (2) or infarction (1), viral hepatitis (1), secondary neoplasm (10), unknown (3). Second tumors wereMDS (4), acute leukemia (AL) (1), non-Hodgkin lymphoma (1), carcinoma (4). The 10-year OS and FFS in an intention-to-treat basis were 51.5% and 42.5%, respectively. The 10-y OS and 10-y FFS for patients transplanted for progressive lymphoma was 53.1%. and 43.8%; for Rel 57.7% and 45.4% ($p<0.05$ and $p>0.05$); for e-Rel 57.0% and 43.9%; for l-Rel 56.1% and 49.4% ($p>0.05$). In unvaried analysis the factors correlated to OS were status of disease at transplant ($p<0.05$), and at HDS start ($p<0.05$), treatment response (RC vs. non-RC) ($p< 0.01$), high vs. normal LDH ($p<0.01$), PS ($p<0.05$). In multivariate analysis the factors turning out significant were treatment response (HR=0.2, $p<0.05$) and high vs. normal LDH (HR 1.8; $p<0.05$). The treatment related mortality was 6.8% The 10-year cumulative risk of MDS/AL was 7.3%.

Conclusions: HDS followed by ASCT is an efficacious salvage treatment for relapsing/refractory HD, with more than half patients surviving 10 y ore more. The feasibility is proven, and the cumulative incidence of 2ary MDS/AL inthe range of the reported literature for salvage treatment for HL.

166 PVAG – A NEW REGIMEN IN ELDERLY PATIENTS WITH HODGKIN LYMPHOMA

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Introduction: About 20% of patients (pts) diagnosed with Hodgkin lymphoma (HL) are > 60 years (yrs) old, 7% > 70 yrs old. While pts aged 60 – 65 yrs with early stage HL have a comparably good treatment outcome, elderly pts with advanced stages demonstrate roughly 50% survival at 3 yrs. In pts > 70 yrs old, treatment outcome is even worse. The most important factor for this poor prognosis appears to be the poor tolerability of chemotherapy, causing substantial dose reduction in rather 50% of elderly pts.

Methods: In 2004-2007, the GHSG performed a multicentre trial to investigate a new first-line regimen in elderly pts (60-75 yrs) with advanced stages HL. The study was aimed to improve the standard regimen (ABVD) by lowering treatment toxicity without compromising efficacy. For this reason, bleomycin and dacarbazine were substituted in the newly designed regimen containing prednisone, vinblastin, adriamycin, and gemcitabine (PVAG). Pts received either 6 cycles PVAG in case of complete remission (CR) after 4 cycles, or 8 cycles in case of less than CR at time of interim staging. Radiotherapy was given to sites of residual disease. Chemotherapy was applied in a 21 days interval.

Results: A total of 61 pts were recruited in 35 collaborating centres. At this point of time, 47 pts with a median age of 69 yrs are available for primary response data. After a median observation time of 7 months, 38 pts (81%) showed CR or partial response, 5 pts showed no change or progressive disease. 2 pts stopped the therapy because of intolerable toxicity, 2 pts died. Dose limiting toxicities occurred in 4 pts (mainly leucopenia). Severe adverse events were observed in 19 pts, caused by protocol according hospitalisations in 18 pts. The majority of pts received the full dosage on time.

Conclusion: With a generally improved prognosis for patients with HL, interest has increasingly focused on high-risk groups such as elderly patients. PVAG could be demonstrated as safe and effective in this cohort. Because of this promising results, the protocol will be further investigated in adult patients with intermediate stages HL (18-60 yrs). Full data set will be presented in summer 2008.

167 EARLY REPORT ON THE ACTIVITY OF LENALIDOMIDE IN CHEMOTHERAPY-REFRACTORY HODGKIN LYMPHOMA PATIENTS

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Lenalidomide is an immunomodulatory drug with multiple properties including inhibition of TNFalpha and VEGF (vascular endothelial growth factor), modulation of T-cell activity and impact on the microenvironment. These characteristics suggest that lenalidomide may play a role in the treatment of Hodgkin Lymphoma (HL), since Hodgkin cells are highly dependent on their microenvironment. To investigate the activity in HL, lenalidomide was provided in a named patient program. Patients were eligible if they had active disease and no curative therapeutic options. Lenalidomide was given at 25 mg daily for 21 days, followed by one week rest. Response was assessed according to Cheson criteria. So far, eight are available for safety and efficacy after two cycles of Lenalidomide. Seven were refractory to prior chemotherapy, and one had an early relapse (8 weeks) after allogeneic transplantation. Six patients were male, the age ranged from 20–64 years. The median number of prior treatments was 4 (range 3-7), all patients had received radiotherapy and autologous stem cell transplantation, and two had received an allogeneic transplant. Disease stage was stage II in two patients, stage III in one patient, and stage IV in five patients. Six patients suffered from B-symptoms. Three patients achieved a partial remission and three patients had stable disease as determined by CT. B-Symptoms resolved in all patients. No severe hematological or non-hematological toxicity was documented. Treatment is ongoing in all patients. Plasma samples before treatment and after cycle two have been stored and cytokine levels will be presented. These data indicate that lenalidomide is active in heavily pretreated patients with progressive, refractory HL. It is too early to judge on the duration of the responses. Since therapeutic options in these patients are very limited and their prognosis is very poor, Lenalidomide warrants further evaluation in this setting. The lack of side effects suggest that higher doses might be tolerated in HL patients.

168 CLINICAL CHARACTERISTICS AND OUTCOME OF 290 PATIENTS (PTS) WITH HODGKIN'S DISEASE AND HIV INFECTION (HD-HIV) IN PRE- AND HAART (HIGHLY ACTIVE ANTIRETROVIRAL THERAPY) ERA.

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Background: HD-HIV pts have clinical aggressive characteristics (i.e. advance stage, B symptoms and extranodal involvement) leading to a poor outcome despite the use of standard chemotherapy. The introduction of HAART has improved the survival of AIDS pts. The aim of our study was to compare pathological, clinical characteristics and outcome of HD-HIV in prior-HAART (naïve pts) and HAART era (HAART pts).

Material and methods: We collected data of 290 pts with HD-HIV diagnosed and treated in several institutions in Italy and France from 1983 to 2007.

Results: HAART pts were significantly older ($p<0.0001$), had less frequency of B symptoms ($p=0.03$), and a higher level of leukocytes ($p=0.02$), neutrophyl cell count ($p=0.02$) and haemoglobin level (p 0.03). In multivariate analysis, the following factors were associated with a shorter survival: histological subtype, extranodal involvement, B symptoms, the prior use of HAART. Factors associated with a shorter time to treatment failure (TTF) in multivariate analysis were International Prognostic Score, the use of HAART, the alcaline phosphatase level.

Conclusions: In our experience, the use of HAART significantly improves the outcome of HD-HIV pts. In our opinion, stratification of patients by prognostic factors of HD and HIV infection is mandatory in order to identify those pts who could benefit by an aggressive chemotherapy regimen similar to that used in HD of the general population.

169 ATTITUDES AND BELIEFS TOWARDS SURVIORSHIP ISSUES IN HODGKIN'S DISEASE (HD). RESULTS OF FOCUS GROUP DISCUSSIONS WITH PATIENTS TREATED AT STANFORD UNIVERSITY

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Background: The vast majority of patient's (pts) treated for HD are cured with current treatment strategies. Recently the Institute of Medicine has issued a directive for survivorship care stating that the care of these pts needs to be focused and geared to address specific issues (therapy and non therapy related) as they transition from being cancer pts to cancer survivors.

Methods: We conducted focus group discussions and distributed surveys to a cohort of pts with HD who had completed therapy at least 3 years ago. The aim of these discussions was to find out what attributes of a survivorship care plan would be most important to our survivors, assess the likelihood of compliance in a dedicated Survivorship Care Clinic and how this could be optimized and determine attitudes regarding enrollment in future research studies. 40 pts were contacted via telephone with the goal of having four groups balanced for age, gender, geography and time since treatment.

Results: 30 pts (17 male and 13 female) median age 46 y (range: 35-76) participated in 4 focus groups led by professional moderators. Median time since treatment was 10 y (range: 3-40). 25 pts had been treated with the Stanford V regimen (initiated 1989) and 5 on earlier protocols. Seven pts had relapsed and had received salvage therapy. Levels of interest in response to survey questions are shown in the table.

Level of Interest

	Slight/Moderate N	High/Enthusiastic N
Attributes of Survivorship Care		
Risk of relapse	8	22
Risk of second cancer	4	26
Effects on normal organs	5	25
Psychological aspects	15	15
Social functions	17	13
Participation in research	4	26
Models of Survivorship Care		
Physician led	10	20
Nurse led	17	13
Shared with primary MD	12	18
Virtual web based	16	14
Receiving a Survivorship Care Plan		
Treatment Summary	1	29
Personalized care plan	2	28
Method of information delivery		
Web based or DVD	8	22
Dedicated Survivorship House	22	8

Conclusions: Receipt of a treatment summary and a personalized survivorship plan was highly desired by participants Our pts, who were highly selected were more interested in learning about risks to their ongoing physical health than psychological or social function. Most pts preferred physician led models (oncologist or shared with primary care) and were highly motivated and interested in research participation. Web or DVD based resources as a method to obtain relevant information was preferred over a dedicated survivorship house concept. These results will be utilized in prioritizing our efforts towards a formal survivorship program for HD pts.