

session 12 – hodgkin's lymphoma

115 NEW INSIGHTS IN CLASSICAL HODGKIN LYMPHOMA (CHL) PATHOGENESIS AS REVEALED BY GENE EXPRESSION PROFILING OF MICRODISSECTED HODGKIN/REED-STERNBERG (HRS) CELLS

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Introduction: cHL cell lines, on which previous gene expression studies about cHL were based, may not reflect primary HRS cells in all features, having lost their dependence on the lymph node microenvironment.

Methods: ~1000-2000 neoplastic cells were microdissected from frozen lymph nodes of cHL, lymphocyte-predominant HL (LPHL) and various B non-HLs, and their RNA hybridized to Affymetrix chips after 2 rounds amplification. Expression profiles were likewise derived from HL cell lines and several normal B-cell subsets.

Results and Discussion: On supervised analysis, primary HRS cells upregulated hundreds of genes as compared to cultured ones, including several involved in interactions with the inflammatory background (e.g., chemotaxis and extra-cellular matrix remodelling). On unsupervised analysis, HRS cells built an own, tight cluster, showing on a genome-wide view that cHL represents a distinct entity. This cluster is surprisingly closer to LPHL than to B non-HLs (including primary mediastinal ones), a result also confirmed by supervised approaches. Only few genes showed a consistently different expression in EBV+ vs EBV- HRS cells, suggesting that EBV infection, while important in apoptosis escape of crippled germinal center B cells (the likely HRS cell precursors), does not leave specific and marked transcriptional imprints in the fully blown cHL clone. Primary HRS cells were not consistently similar to germinal center B or plasma cells but, interestingly, shared a more pronounced transcriptional relatedness with CD30+ B cells. Further analyses are ongoing to find genes/pathways of potential pathogenetic importance for HRS cells.

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116 PET-BASED EVALUATION OF RESIDUAL TISSUE IN ADVANCED-STAGE HODGKIN LYMPHOMA: GHSG INTERIM ANALYSIS OF THE HD15 TRIAL

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Introduction: The prospectively randomized HD15 multicenter trial of the German Hodgkin Study Group (GHSG) included advanced-stage Hodgkin Lymphoma patients comparing 8 cycles of BEACOPP^{escalated} with 6 cycles or 8 cycles time-condensed BEACOPP^{baseline}. One other main study endpoint was the prognostic value of ¹⁸F-FluoroDeoxyGlucose (FDG) Positron Emission Tomography (PET) following chemotherapy. The aim was to specify the negative predictive value of PET (NPV) in patients with residual tumour mass after chemotherapy.

Methods: Entry criteria for the PET question were partial remission (PR) after the end of chemotherapy with at least one involved nodal site measuring more than 2.5 cm in diameter by computed tomography (CT). Exclusion criteria included diabetes, elevated blood sugar levels and skeletal involvement with risk of instability. Calculations were restricted to those cases with either Progressive Disease (PD) or relapse within 12 months after PET or at least 12 months of follow-up. A total of 275 patients were eligible for this analysis. The assessment was based on those patients confirmed by an expert panel as being PET-negative. CT verification was performed to identify false positive PET findings. The NPV was defined as the proportion of patients without progression or relapse within 12 months.

Results: 9/216 patients with PET-negative residues and 9/59 patients with PET-positive residues had PD or relapse within one year of follow-up. The NPV was 0.958% (95% CI 0.931 - 0.985%). In 244/245 cases with PET-negative residual masses, no irradiation was given. In the 62/66 cases with PET-positive residues, additional radiotherapy was performed. Progression/relapse rates were significantly different between those patients with residual mass being PET-negative or PET-positive (P=0.0053). PET-negative patients, who were assessed as partial response by CT, had a prognosis similar to those

in complete remission. There was no significant difference in the progression free survival in this trial and the prior GHSG trials HD12 (arms pooled) and HD9 (arm C) for advanced-stage HL (P=0.266). Importantly, the proportion of patients receiving radiotherapy decreased from 70% (HD9-C) to 39% (HD12) and 12% (HD15).

Discussion: The high NPV of PET suggests that radiotherapy following 6 or 8 cycles of BEACOPP might be restricted to those patients who are PET-positive after chemotherapy.

117 INVOLVED-NODAL RADIOTHERAPY: CAN WE SAFELY REDUCE THE FIELD SIZE FOR LIMITED STAGE HODGKIN LYMPHOMA TREATED WITH COMBINED MODALITY THERAPY?

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Background: Combined modality therapy has been the standard of care for limited stage Hodgkin lymphoma (HL). Radiotherapy has evolved from extended-field (EFRT) to involved-field radiotherapy (IFRT), lowering toxicity whilst maintaining high cure rates. Recent publications recommend a further reduction in field size to involved-nodal radiotherapy (INRT). We sought to determine if field size can be reduced from IFRT to INRT whilst maintaining treatment efficacy.

Material and Methods: 325 consecutive patients with limited stage HL diagnosed between May 1989 and April 2005 were treated with combined ABVD + radiotherapy. According to prospectively defined protocols, patients were treated with EFRT until 1996, IFRT from 1996 to 2001, and INRT from 2001. Exclusion criteria were age <16 y, non-ABVD equivalent chemotherapy, >4 cycles of chemotherapy, and use of PET to guide treatment.

Results: At diagnosis, the median age was 32 y (16-81); 52% were male; Ann Arbor stage was IA in 29% and IIA in 71%; and 10% had extra-nodal disease. Chemotherapy consisted of 2 cycles of ABVD-like chemotherapy in 95%; 3 cycles in 3%; 4 cycles in 2%. Three radiotherapy treatment groups were identified: EFRT, 127 (39%); IFRT with 10 cm margin, 96 (30%); INRT with 5cm margin, 102 (31%). Median follow-up times (months) were: EFRT, 137 (range 14-219); IFRT, 89 (23-137); INRT, 48 (18-75). Median time to relapse was 37 (10-106) months. 12 relapses occurred (4%): EFRT, 4; IFRT, 5; INRT, 3 (P=0.9). Loco-regional relapse (LRR) occurred in 5 patients (2%): EFRT, 3; IFRT, 2; INRT, 0. No marginal recurrences occurred. Distant-only relapse occurred in 7 (2%), and was less common after EFRT (1; INRT, 3; IFRT, 3). For all patients, progression-free survival (PFS) was 97%, and overall survival (OS) was 95%, at 5 years. At 10 years, PFS and OS were 95% and 90%, respectively.

Conclusions: Reducing the radiation field size to INRT has not been associated with increased risks of LRR or marginal recurrence, when used in conjunction with effective chemotherapy for limited stage HL.

118 DEFINING A POPULATION OF HODGKIN LYMPHOMA PATIENTS FOR NOVEL THERAPEUTICS: AN INTERNATIONAL EFFORT

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Background: It is challenging to develop new drugs in Hodgkin lymphoma (HL) based on success with primary treatment and salvage with high dose chemotherapy and autotransplantation (AHCT) in a subset. Interest in new therapeutics stems from a desire for more effective salvage treatment for ~15% patients and, potentially, to reduce acute and chronic toxicity of current, curative therapy for the majority of patients. To better assess the unmet need among relapsed/refractory pt and define a population for trials of new agents, five transplant centers agreed to pool their data for an evaluation of overall survival (OS) in pt relapsed after AHCT.

Methods: Anonymized data for pt age, gender, transplant date, preparatory regimen, date of progression after AHCT, and date of death were requested to evaluate OS according to the time from AHCT to disease progression. Time to progression after AHCT was grouped as 0-3 months (m), >3-6 m, >6-12 m and >12 m.

Results: DATA from three centers are reported (n=241) and data from 2 additional centers (n=128) will be available for presentation. Selection for AHCT was

center-dependent but primarily represented pt <60 y with stable or responding disease after their last therapy and prior to AHCT. Relapses after AHCT were distributed as follows: 0-3 m (23%), >3-6 m (20%), >6-12m (30%) and >12 m (27%) for Centers 1-3. Median OS by center and time to relapse after AHCT were:

Time after AHCT (months)	Center 1 N=66	Center 2 N=66	Center 3 N=109
	(N Patients)	Overall Survival in Months	
0-3	(14) 4	(19) 13	(19) 8
>3-6	(16) 12	(18) 22	(15) 15
>6-12	(16) 7	(19) 46	(38) 21
>12	(17) 25	(10) NR	(37) 48

Evaluation of overall results by time of AHCT before 1990, 1990-2000 and >2000 showed no difference in any of the Centers, indicating the relative stability of OS after relapse from AHCT during the elapsed time.

Conclusions: Pt relapsing within 6 m of AHCT have brief OS and an unmet need for novel therapeutics. Better definition of OS in the distinct subgroups with the addition of data from the 2 remaining centers and pooled data will provide a valid historical control group for clinical trials of new agents.

119 SECONDARY MALIGNANCIES IN PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN'S LYMPHOMA TREATED WITH AN AUTOLOGOUS STEM CELL TRANSPLANTATION. AN ANALYSIS OF THE LYMPHOMA WP OF THE EBMT

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Background: Autologous stem cell transplantation (ASCT) has been used as a standard treatment in the management of patients (pts) with relapsed/refractory Hodgkin's lymphoma (HL) in the last few decades. At the moment only little data is available on incidence of secondary malignancies (SM) among this group of pts.

Material and Methods: We analysed HL pts treated with first ASCT and registered in the European Group for Blood and Marrow Transplantation for occurrence of SM. Further inclusion criteria were: age at ASCT ≥18 years and time of ASCT between 1985 and 1995. Univariate and multivariate analyses of risk factors for SM were performed.

Results: 2289 pts were included (median age at ASCT 30 years, range 18–70); 61.5% pts were male; 76.9% of pts were in complete or partial remission at the time of ASCT. BEAM was the conditioning regimen most frequently used (57.3%) followed by CBV (29.4%); TBI was given to 4.6% of pts. Median follow-up for all pts was 49 months (range 0 – 240). Progression free survival and overall survival at 10 years were 40.7% and 47.9%, respectively. 43.5% of pts relapsed after a median time of 8.6 months post-ASCT and 48.7% of pts died. The main causes of death were relapse/progression (70.6%), transplant related mortality (23.4%) and SM (3.8%). SM was diagnosed in 86 pts (3.9%): solid tumours (ST) in 38 pts (1.7%), MDS/acute leukaemias (AL) in 40 pts (1.7%) and NHL in 6 pts (0.5%). Cumulative risk at 10 years for SM was 4.5%, for solid tumours 2.2% and for MDS/AL 1.8%. The significant risk factors in multivariate Cox regression analysis for SM were age at ASCT >40 years, time from diagnosis to ASCT >48 months and conditioning with CBV; for ST - age at ASCT > 40 years and for AL - age at ASCT >40 years, time from diagnosis to ASCT >48 months, conditioning with CBV and TBI in conditioning (p<0.05).

Conclusion: ASCT remains the standard treatment for pts with refractory/relapsed HL. The cumulative risk for SM among evaluated patients is higher compared with that reported among HL patients after first line treatment and is expected to increase over time.