Session 15: Hodgkin lymphoma

159 GENETIC POLYMORPHISMS INFLUENCE THE RISK OF HODGKIN'S LYMPHOMA

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Background: The etiological factors behind Hodgkin's lymphoma (HL) are not clearly established. Identifying key factors behind lymphomagenesis is warranted to better understand the processes behind the development of lymphoma and thereby possibly discover new prophylactic- and treatment strategies. Studies have shown that regulation of proteins involved in the immune response, i.e. TNFs, interleukins and other cytokines, may be of importance to promote or suppress lymphomagenesis. Additionally, altered function of proteins involved in the metabolism of carcinogenic compounds and drugs may influence the level of exposure of such compounds, and thereby enhance or lower their effect on biological processes in humans. Genetic polymorphisms (SNPs, deletions, etc) have been found to alter the level and function of such proteins, and may thereby influence the risk and prognosis in HL and NHL.

Material and Methods: We genotyped polymorphisms in several genes encoding cytokines and metabolizing enzymes in 232 HL patients and 1056 healthy controls. The genes investigated were encoding the cytokines IL-10 (rs1800890) and IL-4 (rs2243248), the cytokine receptor IL-4R, (rs2107356), and the metabolizing or drug transporting enzymes CYBA (rs 4673), ABCC2 (rs17222723), GSTP1 (rs1695), GSTA1 (rs3957357), UGT1A1 (tandem repeats), GSTM1 (deletion), and GSTT1 (deletion). The DNA segments of interest were amplified by PCR with FAM-dyed immunoflouresence and the genotypes were analyzed with the standard multicapillary DNA sequencing instrument MegaBACE™ 1000 DNA Analysis System (Amersham Biosciences, Oslo, Norway). Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using logistic regression.

Results: Polymorphic variants in three genes (IL-10, GSTP1, and GSTT1) were associated with an increased risk of HL.In IL-10, the AA genotype compared to AT/TT (OR 1.48 (95% CI 1.00-2.19), p=0.048; GSTP GG compared to AA/AG (OR 1.51 (95% CI 1.03-2.22), p=0.04; and in GSTT1 the deleted variant compared to the undeleted (OR 3.40 (95% CI 2.22-5.20), p<0.001.

Polymorphism	Genotypes	OR (95%CI),	p-value
IL-10 (rs1800890)	AA vs. AT/TT	1.48 (1.00-2.19),	0.05
GSTP1 (rs1695)	GG vs. AG/AA	1.51 (1.03-2.22),	0.04
GSTT1 (no rs)	del vs undel	0.62 (0.31-1.22),	<0.001

Conclusion: We find that polymorphisms in genes coding for IL-10 (rs1800890), GSTP1 (rs1695), and GSTT1 (deleted/undeleted) are associated with increased risk of HL. These gene product variants are associated with inferor immune regulatory function (IL-10) and enzymatic degradation of toxic compounds (GSTTP, GSTT1), respectively.

160 DURABLE COMPLETE REMISSIONS IN A PIVOTAL PHASE 2 STUDY OF SGN-35 (BRENTUXIMAB VEDOTIN) IN PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN LYMPHOMA (HL)

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Introduction: CD30 expression by Reed-Sternberg cells is a defining feature of HL. SGN-35 comprises an anti-CD30 antibody conjugated by a plasma-stable linker to the potent antimicrotubule agent, monomethyl auristatin E (MMAE). SGN-35 selectively induces apoptotic death of CD30+ cells by binding, internalizing, and releasing MMAE.

Methods: A pivotal, phase 2, single-arm, multicenter study evaluated the efficacy and safety of SGN-35 in patients (pts) with relapsed or refractory HL after autologous stem cell transplant (auto-SCT). Pts received SGN-35, 1.8 mg/kg q3 weeks (wks) as a 30?min. outpatient IV infusion for up to 16 cycles. The primary endpoint was the objective response rate (ORR) per an independent review facility (IRF) according to Cheson 2007.

Results: 102 pts were enrolled; 53% female, median age was 31 yrs (range 15C77). Pts had received a median of 3.5 (range 1C13) prior systemic therapies excluding auto-SCT.71% of pts had primary refractory disease and 42% had not responded to their most recent prior therapy. ORR per IRF was 75% (76 of 102 pts) with complete remissions (CRs) in 34% of pts (n=35). At the time of database lock (August 2010), median duration of follow up from first dose was ~9 months (for responders). Median duration of response for pts with CR per IRF has not yet been reached (range 0.3+ to 61.4+ wks); follow up continues and 6+ months of additional data will be available for presentation. Treatment-related AEs of any grade in ≥ 15% pts were peripheral sensory neuropathy, nausea, fatigue, neutropenia, and diarrhea. AEs ≥ Grade 3 in ≥ 5% of pts were neutropenia, peripheral sensory neuropathy, thrombocytopenia, and anemia.

Conclusions: With manageable AEs, single-agent SGN-35 induced objective responses in 75% of pts with relapsed or refractory HL. In this heavily pretreated population, 35 of 102 pts (34%) achieved a durable CR, with more than 65% of pts remaining in CR.

161 BIOMARKER ANALYSIS OF PIVOTAL PHASE II STUDY OF ORAL PANOBINOSTAT (PAN) IN RELAPSED/REFRACTORY HODGKIN LYMPHOMA (HL) PATIENTS FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANT (ASCT)

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Background: Panobinostat (PAN) is an oral pan-histone deacetylase inhibitor (pan-HDACi). Thymus and Activation-Regulated Chemokine (TARC) is a major mechanism by which Reed-Sternberg cells drive intratumoral accumulation of reactive cells. TARC levels decrease with HDACi in HL cell lines and reflect disease activity in patients (pts). In a pivotal HL study, PAN achieved durable responses in heavily pretreated relapsed/refractory pts after ASCT. Prospective analysis of TARC levels was done to identify biomarkers for disease activity and to assess correlation with treatment response to PAN.

Methods: PAN was administered 40 mg TIW, every week in 21-day cycles. Response was assessed every 2 cycles by CT/MRI scan. Blood was collected at screening, days 5, 8, and 15 of cycle 1, day 1 of cycles 2-4, and end of treatment. Milliplex Map Human Cytokine/Chemokine panel II (Millipore) was used to analyze TARC.

Results: Of 129 treated pts, 74% had tumor reduction and 35 achieved response: 5 complete (CR), 30 partial (PR). Samples were collected from 117 pts for analysis. Baseline TARC levels were similar across pts with CR, PR, SD, and PD. Reduction of TARC was observed as early as cycle 1 day 8. Percent change, calculated as a geometric mean of ratios of TARC level at cycle 1 day 15 to baseline, showed a reduction of TARC level to 72% in CR, 78% in PR, 90% in SD, and no change in PD pts. Pts with higher reduction were at less risk compared to pts with lower reduction of TARC, hazard ratio 2.22 [CI 95%; 1.27, 3.90] and median PFS in the high reduction group was 9.9 months vs 4.9 months for the low reduction group. Similar trends were observed at other time points.

Conclusion: Early TARC reduction was observed post treatment with PAN in HL pts with disease control. TARC reduction at C1D15 was highest in patients achieving CR and PR, providing further evidence to support the MoA of HDACi in HL. Further analysis is ongoing to correlate changes in TARC vs time to response and target lesion reduction which may support TARC as a biomarker for monitoring HL response to PAN.

162 EARLY DETERMINATION OF TREATMENT SENSITIVITY IN HODGKIN LYMPHOMA: FDG-PET/CT AFTER ONE CYCLE OF THERAPY HAS A HIGHER NEGATIVE PREDICTIVE VALUE THAN AFTER TWO CYCLES OF CHEMOTHERAPY

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Introduction: The high prognostic value of FDG-PET/CT performed after two cycles of chemotherapy for Hodgkin lymphoma (HL) is well known. However, PET/CT after two cycles of therapy still yields false positive and false negative results. Furthermore, a therapy modification based on treatment sensitivity should be carried out as early as possible in order to avoid development of chemotherapy resistance and avoid unnecessary and ineffective treatment. The aim of this study was to compare the prognostic value of FDG-PET/CT after one and two cycles of chemotherapy for HL.

Materials and Methods: A total of 64 HL patients, prospectively enrolled in three international centers. Stage I-IIA disease were present in 27 and stage IIB-IV disease in 37 patients. 59 patients received ABVD and 5 patients received BEACOPPesc chemotherapy. 22 patients received consolidation radiotherapy. All patients had a PET/CT study at baseline and after one cycle, 59 patients after two cycles as well. All interim scans were scored blinded to treatment outcome by experienced PET readers, according to the 5-point Deauville criteria. A score of 1-3 was considered a negative result, and a score of 4-5 a positive result.

Results: Overall, 86% of patients achieved a CR after first-line treatment. At a median FU of 23 months, 12 patients had experienced a PFS event. PET was negative in 45 (70%) patients after the first cycle (2-year PFS = 100%) and 19 (30%) were PET-positive (2-year PFS = 34%). 50 (85%) patients were PET-negative after the second cycle (2-year PFS = 89%) and 9 (15%) were PET-positive (2-year PFS = 22%). All patients who were PET-negative after the first cycle stayed PET-negative after the second cycle and entered a durable CR.

Conclusions: Patients responding well to HL chemotherapy can be accurately identified by PET/CT after only one cycle of chemotherapy, and the negative predictive value is higher after one cycle than after two cycles. De-escalation treatment strategies may be better tailored to well responding individuals based on PET/CT results after one cycle than after two cycles of chemotherapy.

163 MULTICENTRE CLINICAL STUDY WITH EARLY TREATMENT INTENSIFICATION IN HIGH-RISK HODGKIN LYMPHOMA (HL) PATIENTS, WITH A POSITIVE FDG-PET SCAN AFTER TWO ABVD COURSES – GITIL HD0607 STUDY

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Background: Interim PET scan after 2 CT courses (PET-2) is the most powerful predictor of treatment outcome in advanced-stage, ABVD-treated HL patients (pts.). Although retrospectively demonstrated, the overall efficacy of a PET response-adapted treatment for ABVD-treated advanced-stage HL is still prospectively unproven.

Methods: In the HD 0607 study, after 2 ABVD PET-2+ pts are randomized to BEACOPP escalated (Be) plus BEACOPP baseline (Bb) (4+4 courses) versus Be+Bb (4+4) plus Rituximab. PET-2 negative pts continue with 4 ABVD +/- consolidation radiotherapy on the sites of initial bulky disease. All the non-negative PET-2, defined as scans with any residual FDG uptake in any site outside the physiological areas of the tracer concentration, are uploaded in a website for review by a panel of 6 nuclear medicine experts. Scans are interpreted by visual assessment according to the Deauville 5-point scale.

Results: From 07/2008 till 01/2011,279 advanced-stage (IIB-IVB) pts were consecutively enrolled and 252 performed PET-2. Overall, 95/252 PET-2 were considered non-negative and reviewed: 46/95 turned out positive (score 4-5) and 49/95 negative (score 1-3). The median time from PET uploading in the website to review was 1.36 days. The binary concordance rate among reviewers was very good, and ranged from 0.79 to 0.90 (Cohen's k coefficient); overall concordance rate was 0.84 (Krippendorf's alpha). 104/279 pts completed the scheduled treatment and are suitable for the analysis after a mean follow-up of 190 days from the end of treatment: 17 with a positive and 87 with a negative PET-2. In 17 PET-2+ pts, 13 showed a single site, 4 ≥ 2 sites of persistent FDG uptake. In the 13 single site-PET-2+ pts, the most frequent site was mediastinum (8), upper cervical (2), supraclavear (1), and iliac (2) nodes. 15/17 PET-2+ pts became negative at the end of treatment. The 1-y PFS was 88.2%, 94.3% and 93.3% for PET-2+, PET-2- p, and for the entire population, respectively.

Conclusions: These preliminary findings seem to show that 1) PET scan online review system is feasible and timely available; 2) concordance rate among reviewers is very good; 3) most PET-2+ pts after 2 ABVD courses could enter a sustained CR if promptly rescued with BEACOPP.

164 IGEV VS. IGEV+BORTEZOMIB (VELCADE™) BEFORE HIGH-DOSE CONSOLIDATION THERAPY FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IN RELAPSED OR REFRACTORY HODGKIN LYMPHOMA (HL): A RANDOMIZED PHASE II TRIAL OF THE FONDAZIONE ITALIANA LINFOMI

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Background: Complete remission (CR) at ASCT is the mainstay of therapeutic success in relapsed/refractory HL. IGEV CR rate approaches 50%. As bortezomib-gemcitabine synergism is suggested, we combined IGEV with bortezomib (B-IGEV) to test the CR rate compared to IGEV alone.

Material and methods: Pts were randomly assigned to 4 courses of 3-week IGEV or IGEV + bortezomib at 1,3 mg/m^2, on days 1, 4, 8- both. Peripheral stem cell harvest was planned after the 3th cycle. Primary endpoint was CR rate (FGD-PET negativity), secondary were comparative toxicity, mobilization potential and survival rates.

Results: Eighty pts entered the trial from Feb 2008 to Feb 2010: 40 assigned to IGEV and 40 to B-IGEV. Clinical features were well balanced. In the whole series: med age 35.5 (18-64), M/F 46/34, I-II/III-IV stage 38/42, relapsed/refractory 43/37, bulky 35. Among 75 evaluable pts, response rate (RR) was 59%, CR rate 43%. CR rate was 45% in IGEV (17/38) and 41% (15/37) in B-IGEV, respectively. Therapy was well tolerated, and no substantial differences were documented between the two arms. Peripheral neuropathy and febrile neutropenia never exceed grade II. 36 patients (45%) needed red blood cells and/or platelet transfusions. Whole series 1-year PFS- OS are 48-94%, respectively.

Conclusions: This trial confirm IGEV activity as pre-transplant induction in relapsed/refractory HL. The addition of bortezomib to IGEV did not improve the RR compared to IGEV. Good safety profile may prompt testing new different active drugs in HL to possibly improve on the efficacy of IGEV alone.

165 PARENTHOOD IN SURVIVORS OF HODGKIN LYMPHOMA (HL): AN EORTC-GELA GENERAL POPULATION CASE-CONTROL STUDY

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Background: We investigated the impact of HL on parenthood, comparing HL survivors with matched general population controls (UNECE Generations and Gender Survey), available for France and The Netherlands.

Material and methods: Surviving and traceable patients treated in 1964-2004 in nine multicenter trials were sent a life style questionnaire in 2009, including questions on parenthood. Responders aged ≥15 at treatment were matched (1:3-4) for sex, country, education and year of birth (10 year cohorts). Controls were given an artificial date of diagnosis, the same as their matched patient. Presence of biological children after treatment was determined. Conditional logistic regression analysis was used.

Results: Of 3604 patients contacted in 5 countries, 1910 (53.0%) responded. 1654 French and Dutch patients were matched with 6414 controls. Median follow-up was 14 (range 5-44) years. Before treatment, 45.7% of patients and 48.8% of controls had children. After treatment, the Odds Ratio (OR) for patients to have children was 0.77 (95% CI 0.68-0.87; p<0.001). OR did not change with correction for presence of children before, age at start of or treatment period. OR was 0.84 (95% CI 0.70-1.00; p=0.06) for males; it was 0.64 (95% CI 0.52-0.77; p<0.001) for females corrected for age at start of treatment.

Of 898 patients childless before treatment, 60.1% tried to have children and 46.7% succeeded, compared to 49.3% in 3196 childless controls (OR=0.87; 95% CI 0.74-1.01, p=0.08). Among 756 patients with children before treatment 16.8% attempted post-treatment parenthood; 12.4% succeeded compared to 22.2% of 3218 controls with children before treatment (OR=0.49; 95% CI 0.38-0.63, p<0.001). Post-treatment adoption concerned 26 patients (1.6%) compared to overall adoption in 59 controls (0.9%) (OR 1.78; 95% CI 1.10-2.87; p=0.02).

Conclusions: Survivors of Hodgkin lymphoma had slightly but significantly less children after treatment than general population controls. The difference only concerned patients who had children before treatment. However, in patients who attempted post-treatment parenthood three-quarters succeeded.

166 GONADAL FUNCTION IN WOMEN AFTER TREATMENT OF EARLY UNFAVOURABLE HODGKIN LYMPHOMA (HL). FIRST RESULTS OF THE FERTILITY RESEARCH PROJECT WITHIN THE 5TH TRIAL GENERATION, GERMAN HODGKIN STUDY GROUP (GHSG)

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Background: The incidence of gonadal dysfunction and the improvement of fertility protection strategies in young HL patients are the focus of current research. In the HD14 trial for early unfavourable HL, improved progression free survival with escalated BEACOPP compared to ABVD was expected to be compromised by a higher rate of infertility.

Methods: The study included young (18-40 yrs) female patients without progress or relapse, at least one year after therapy. Treatment consisted of 4xABVD (arm A) or 2xBEACOPPesc+2xABVD (arm B) followed by involved field irradiation. Blood samples were drawn to determine follicle-stimulating hormone (FSH), luteinizing hormone (LH), ß-oestradiol, and Anti-Müllerian Hormone (AMH). Furthermore, self-administered questionnaires to assess fertility, menopausal symptoms (Menopause Rating Scale, MRS), and quality of life were sent to the patients.

Results: Overall, 549 women were addressed and 293 participated (53%). Baseline data revealed no major differences between participating and not participating patients. There were 253 per-protocol treated female patients qualifying for the comparison of the randomized treatment arms (A: 131, B: 122). Follicle-stimulating hormone and AMH values were significantly more favourable in arm A than in arm B. Surprisingly, the rate of regular menstrual cycle after treatment did not differ between the two arms (A: 88% vs. B: 84%). In addition, recovery time to regular menstrual cycle did not differ and lasted one year maximally. Pregnancy and birth rates after therapy were not different (birth rate A: 11% vs. B: 18%). Interestingly, in our Hodgkin cohort all age groups showed motherhood rates which were almost identical to German normal population rates. Menopausal symptoms (MRS) did not differ between the two arms but were increased compared to reference values.

Conclusion: Compared to 4*ABVD, 2*BEACOPPesc+2*ABVD causes measurable changes in FSH and AMH hormone levels. However, the BEACOPP containing regimen was not inferior to ABVD with respect to the clinically outcome parameters fertility and menopausal symptoms. Surprisingly, the motherhood rate after escalated BEACOPP chemotherapy was not impaired even compared to the German control population. Thus, treatment with 2*BEACOPPesc+2*ABVD for early unfavourable HL can be recommended for young women with desire for children.