Session 15: Hodgkin lymphoma

159 GENETIC POLYMORPHISMS INFLUENCE THE RISK OF HODGKIN’S LYMPHOMA
O. E. Yiil, V. Hildem1, E. B. Smelend2, G. Gaudernack3, K. Liestrø1, P. O. Østrom1, H. Holte4
1Dept of Oncology, Oslo University Hospital, Oslo, Norway, 2Inst of Cancer Research, Oslo University Hospital, Oslo, Norway

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 that drive the development of lymphomas 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 progression 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 gene 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 (rs4673), ABCB1 (rs7722723), GSTP1 (rs1695), GSTA1 (rs957357), UGT1A1 (tandem repeats), GSTM1 (deletion), and GSTT1 (deletion). The DNA segments of interest were amplified by PCR with FAM-dyed primers, and the genotypes were analyzed with the standard multiplex 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=0.04; GSTP1 GG compared to AG/AA (OR 1.48 (95% CI 1.00-2.19), 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).

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 inferior immune regulatory function (IL-10) and enzymatic degradation of toxic compounds (GSTTP, GSTT1), respectively.

160 DURABLE COMPLETE REMISSIONS IN A PILOT PHASE 2 STUDY OF SGN-35 (Brentuximab Vedotin) IN PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN LYMPHOMA (HL)
1LymphMyel, MD Anderson CC, Houston, United States, 2Med/Onc, Univ Washington, Seattle, United States, 3Hem/Onc, Loyola Univ Med Ctr, Maywood, United States, 4Hemat, Mayo Clinic, Rochester, United States, 5Sylvestor Cancer Ctr, Univ Miami, Miami, United States, 6Ctr Lymph Cancer, BC Cancer Agency, Vancouver, Canada, 7Hem/Onc, Univ Hosp Cologne, Cologne, Germany, 8Clin Dev, Seattle Genetics, Inc, Seattle, United States

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). Results: 102 pts were enrolled; 53% female, median age was 31 yrs (range 15-77). Pts received a median of 3.5 (range 1.3-13) 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. Conclusion: These preliminary results suggest that SGN-35 may be effective in heavily pretreated patients with HL, 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)
S. Harrison1, A. Hsu1, P. Neeson1, A. Younes2, A. Surena1, A. Engert3, M. Li4, P. Snaps4, R. Bugarin5, C. Le Corre5, D. Williams5, J. Gallagher5, A. Shen6, H. M. Prince1, R. Ritchie2
1Cancer Medicine - Haematology, Peter MacCallum Cancer Centre, East Melbourne, Australia, 2Lymphoma Myeloma, MD Anderson Cancer Center, Houston, United States, 3Hematology, Cambridge University Hospitals, Cambridge, United Kingdom, 4Internal Medicine, University Hospital of Cologne, Cologne, Germany, 5Oncology Biomarker & Imaging, Novartis Pharmaceuticals, East Hanover, United States, 6Oncology BDM, Novartis Institutes for BioMedical Research, Cambridge, United States, 7Oncology, Novartis Pharma AG, Basel, Switzerland, 8Oncology, Novartis Pharmaceuticals, East Hanover, United States

Background: Panobinostat (PAN) is an oral pan-histone deacetylase inhibitor (pan-HDACi). Thymus and Activation-Regulated Cytokine (TARC) is a major mediator 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+21+21 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 1. 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 CYD15 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
M. Hutchings1, L. Kostakoglu1, J. M. Zaucha2, B. Mallowski3, A. Biagg1, I. Danelierowicz2, A. Loff2, L. Specht4, M. Coleman4
1Depts. of Haematology and Oncology, Copenhagen University Hospital, Copenhagen, Denmark, 2Dept. of Radiology, Mount Sinai Medical Center, New York, United States, 3Dept. of Haematology, Medical University Gdansk,
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 - GITL HD0607 STUDY

A. Gallimini1, C. Tarella2, C. Patti3, A. Gianni4, S. Bolis5, L. Trentini6, A. Biggi7, S. Czubar8, M. Menotti9, A. Rambaldi9

1Haem., AO S. Croce, Cuneo, Italy, 2Haem., AO Mauriziano, Turin, Italy, 3Haem., AO Cervello, Palermo, Italy, 4Oncol., Istituto Nazionale Tumori, Milano, Italy, 5Haem., AO San Gerardo, Monza, Italy, 6Haem., AO Padova, Padova, Italy, 7Nucl. Med., AO S. Croce, Cuneo, Italy, 8Nucl. Med., AO Cervello, Palermo, Italy, 9Nucl. Med., Istituto Nazionale Tumori, Milano, Italy

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 HD0607 study, after 2 ABV 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 ABV +/- 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 tracor 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 08/2007 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 (Krippendorff’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 a 2 sites of persistent FDG uptake. In the 13 single site-PET-2+ pts, the most frequent site was mediastinum (8), upper cervical (2), supraclavicular (1), and iliac (2) nodes. 15/17 PET-2+ pts became negative at the end of treatment. The 1-pFS was 88.2%, 94.3% and 93.3% for PET-2+, PET-2-, and for the entire population, respectively.

Conclusions: These preliminary findings seem to show that 1) PET scan online review strategy 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.
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.

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), β-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.