''focus on...'' session: T-cell

092 CORRELATION BETWEEN EPSTEIN-BARR VIRUS (EBV) RNA EXPRESSION AND VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) EXPRESSION IN DIFFERENT SUBTYPES OF PERIPHERAL T-CELL LYMPHOMAS (PTCL) AND PROGNOSTIC IMPLICATIONS

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Background: EBV is known to be associated with various lymphoid malignancies. An up-regulation of VEGF by EBV has been suggested. The aim of this study was to investigate the correlation between the expression of EBER and angiogenic molecules in PTCL and to examine their possible prognostic impact.

Material and methods: Tissue sections from 62 PTCL (36 PTCL-unspecified (PTCL-u), 1 NK/T nasal type, 7 angioimmunoblastic (AIL), 18 anaplastic large cell (ALCL)) were analysed. The expressions of EBV encoded small nuclear RNAs (EBER) and VEGF mRNA were detected by *in situ* hybridization (ISH). The expression of LMP-1 protein was examined by immunohistochemistry (IH). In 44 cases, the expressions of VEGF, VEGF-C, Flt-1, KDR and Flt-4 were also estimated by IH.

Results: EBER expression was detected in 37% of the all PTCL cases (PTCL-u 38 %, AIL 85%, ALCL 16%). Strong EBER positivity correlated to higher VEGF mRNA expression, both in the entire cohort analysed (p=0.02) and separately in PTCL-u (p=0.02). High EBER expression correlated to nuclear Flt-4 expression (p=0.01). Cases showing diffuse expression of VEGF mRNA had significantly poorer event-free (p=0.02) and overall (p=0.04) survival than cases with focal or no expression. Higher EBER expression was correlated with higher IPI (p=0.01), but had no impact on survival when all PTCL cases were analysed together. If analysed separately for PTCL-u, a high EBER expression predicted a poorer event-free survival (p=0.02) and tended to be associated with adverse impact on overall survival (p=0.08).

Conclusions: EBV RNA was detected in 37% of all PTCL cases analysed. Strong EBER expression significantly correlated to higher VEGF mRNA and nuclear Flt-4 expression, suggesting that EBER may up-regulate angiogenic pathways in lymphoma cells. Diffuse VEGF expression was associated with an adverse impact on survival. In PTCL-u, EBER predicted poorer outcome.

093 A NEW PROGNOSTIC MODEL FOR PERIPHERAL T/NK-CELL LYMPHOMAS (PTCLS) FROM PROSPECTIVE MULTICENTER CLINICAL TRIALS

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Background: PTCLs are known to show a worse survival than B-cell lymphomas. There have been few studies on validation of IPI among patients with PTCLs especially in prospective clinical trials, because PTCLs are relatively rare and geographically not equally distributed in the world.

Materials and Methods: JCOG-LSG consecutively conducted 6 multicenter clinical trials for advanced aggressive lymphoma in 1990s, including 4 CHOP-based chemotherapies (JCOG9505, 9506, 9508 and 9809) and 2 second or third generation multidrug combination chemotherapies (JCOG9002 and 9203). Among the whole 1,141 enrolled pts, histopathological specimens from 1,084 pts were reviewed by 6 hematopathologists and each consensus diagnosis was made according to the WHO classification. Major eligibility criteria in those 6 trials were age between 15 and 69 except one trial for elderly pts, intermediate- or high-grade lymphoma by Working Formulation excluding ATLL, LBL, and CTCL. ECOG performance status 4 was excluded.

Results: We analyzed 136 cases of PTCLs, including 18 ALCL, 46 AILT, 53 PTCL-U, 17 extranodal NK/T-cell lymphoma, nasal type (NK/T). Four unfavorable prognostic factors for OS identified by the univariate analysis were low serum total protein (TP) (<6.3g/dl), gastro-intestinal tract involvement, pathological subtype (PTCL-U+NK/T vs. ALCL+AILT) and low serum albumin (<3.7g/dl). Any factors included in IPI or PIT were not significant and neither IPI nor PIT fitted PTCLs well in this study population. In a multivariate analysis, low TP [HR 2.21 (95%CI:1.28-3.83, p=0.004)] and pathological subtype (PTCL-U+NK/T) [HR 1.73 (95%CI:1.08-2.77, p=0.024)] were significant and independent risk factors. We constructed a new prognostic model by combining these prognostic variables: group 1, no adverse factors; group 2, 1 factor; and group 3, 2 factors. This novel prognostic index for PTCLs was able to efficiently identify 3 groups of pts with different outcomes (p<0.0001). For the 49 pts in group 1, the 2-year and 5-year survival rates were 75.5% and 61.2%, respectively; for the 66 pts in group 2, 56.1% and 42.3%; and for the 16 pts group 3, 31.3% and 12.5%.

Conclusions: Our study indicates that TP and pathological subtypes are important prognostic factors in PTCLs. A new prognostic model for PTCLs warrants further validation studies. (Supported by 2S-1, 5S-1, 8S-1, 11S-1,4, 14S-1,4, 17S-1,5)

094 T-CELL LYMPHOMAS IN STUDIES OF THE GERMAN HIGH-GRADE NHL STUDY GROUP (DSHNHL)

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From 1993 to 2006 331 patients (pts) with mature T cell lymphoma were treated on DSHNHL protocols NHL-B1 (98 pts), NHL-B2 (41 pts), highCHOEP phase II/III (74 pts), MegaCHOEP phase II/III (59 pts), and RICOVER60 (59 pts). 207 pts were male, the median age at study entry was 50 years (yrs). LDH was elevated in 34% of pts, 48% had stage III/IV disease, ECOG performance status was >1 in16% and more than one extranodal involvementwas present in 18% of pts resulting in IPI low in 54%, low-intermediate in 24%, high-intermediate in 13%, and high in 9% of pts. Median observation time for all pts was 3.6 yrs. OS and EFS were 65% and 51%, respectively, at 3 yrs. Significant differences in OS were found according to IPI scores. In univariate analyses OS and EFS were significantly influenced by the presence / absence of any IPI factor. In a multivariate COX model the IPI factors except advanced stage (III/IV) remained significant. Interestingly, younger pts (<=60 yrs) with good-risk disease (LDH <= N) showed significantly better 3-yrs-EFS (71 vs. 50%) when etoposide (ETO) was added to CHOP-14 or -21 (p=0.010). Elderly pts (> 60 yrs) did not benefit from addition of ETO; however, there was a trend for better EFS in the elderly if CHOP-14 instead of CHOP-21 was used (p=0.069). Furthermore, in the RICOVER study pts >60 yrs did not show a benefit if 8 instead of 6 courses of CHOP-14 were administered. Overall, OS and EFS for pts with mature T cell lymphoma treated on DSHNHL studies are encouraging. Findings reported earlier for pts with aggressive B-cell lymphomas were also present in pts with T cell lymphoma: 1. CHOEP resulted in superior EFS over CHOP in younger but not in elderly pts, 2. CHOP-14 was superior to CHOP-21 in the elderly, and 3. the administration of 2 further courses of CHOP-14 did not improve outcome over 6 courses. Also, the IPI proved a robust tool to predict OS and EFS in pts with mature T cell lymphoma.

095 MATURE T-CELL LYMPHOMA PATIENTS SHOW HIGH RELAPSE RATES AFTER HIGH DOSE THERAPY FOLLOWED BY AUTOLOGOUS TRANSPLANTATION

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We here report on 298 pts who received ASCT in EBMT centres from 2000 to 2005. Subtypes were anaplastic large cell lymphoma (ALCL, 34.9%), peripheral TCL (54.7%), and TCL unspecified (10.4%). 19 had ALK pos ALCL, 33 ALK neg (52 missing data). Median age was 48 yrs (12%> 60 yrs). 175/228 pts had stage III/IV and 98/186 had an IPI ≥ 2. 61.7% received HDT within 12 months (mo) after diagnosis. Status at ASCT was CR 1 for 34.1%, chemosensitive other than CR1 for 55.6% and refractory/untested for 10.4%. 76.3% received BEAM like regimens. At a median FU of 39 mo 132 pts (44.3%) have relapsed within median 4 mo. 31.8% of these pts were alive at the time of

analysis. Non relapse mortality (NRM) was 9.7%, PFS 46%, OS 60%. In multivariate analysis, the only adverse factor for PFS was refractory disease at ASCT (p=0.002, trends: IPI ≥ 2 [p=0.09], 2 or more previous treatment regimens [p=0.15], age > 60 yrs [p=0.17], and poor performance status [PS, p=0.2]). Associated with a higher NRM were poor PS (p=0.003) and refractory TCL (p=0.01) but not age. The relapse rate was higher for refractory pts (p=0.005), IPI ≥ 2 (trend, p=0.1) and age >60 (p=0.004). Based on these data one may conclude that pts with chemorefractory TCL do not benefit from HDT and ASCT. Despite chemosensitive disease in 84% of pts the relapse rate was higher than 40%. Prospective studies are mandatory to define the group of TCL pts who will be cured by ASCT and to select pts who will need other approaches.

096 PHASE II STUDY OF DENILEUKIN DIFTITOX WITH CHOP IN PTCL

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Denileukin diftitox (Dd) is a recombinant fusion toxin which targets the interleukin-2 receptor and has demonstrated a 50% response rate in patients with relapsed/refractory PTCL. Because of poor overall outcomes for patients with PTCLu and other aggressive T-cell lymphoma subtypes, we initiated a Phase II study to evaluate the safety and efficacy of the combination of Dd with CHOP as first line therapy in patients with PTCL. Dd was admnistered at a dose of 18 ug/kg/day for days 1,2 and CHOP on day 3 every 21 days for 6 cycles. All patients received G-CSF support. Of 47 enrolled patients, the median age was 52. Twenty-two patients had PTCLu, 12 had angioimmunoblastic T-cell lymphoma, 6 had ALCL, and 7 had other subtypes. Thirty-seven patients were evaluable for response. The overall response rate was 89% with 29/37 (78%) CR, 4/37 (11%) PR, 3/37 (8%) SD. Eleven of 37 responders (30%) have progressed, and the median response duration has not been reached. The median PFS is 17 mo. Twelve patients have died, including one due to tumor lysis and rhabdomyolysis and one due to unknown causes. Nineteen patients experienced one or more grade 3 or 4 hematologic toxicities and 16 experienced one or more grade 3 or 4 nonhematologic toxicity. Six patients discontinued for AE's all occurring prior to cycle 2. These included infusion related anaphylaxis, elevated LFTs and line sepsis (1 patient). THe median survival has not been reached. In conclusion, the combination of Dk with CHOP as first line therapy for patients with aggressive T-cell lymphomas was well-tolerated and associated with a high overall response rate.

097 INCREASED RISK TO DEVELOP ANAPLASTIC LARGE CELL LYMPHOMA IN WOMEN WITH BREAST IMPLANTS

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Background: Recently, we identified two patients with anaplastic large T-cell lymphoma (ALCL, ALK1-) in the fibrous capsule of silicone breast prosthesis, placed for cosmetic reasons. Similar cases have been reported in the literature. An increased risk of ALCL in patients with breast prostheses has been speculated but no studies have been conducted so far.

Methods: A comprehensive search (PALGA) for all patients with lymphoma in the breast diagnosed between 1990 and 2006 was performed in the Netherlands. Eleven patients with ALCL in the breast were retrieved for whom complete clinical and pathological information were collected. Subsequently, a matched case-control study was performed with 3-7 controls with other lymphomas in the breast, matched on year and age of diagnosis. Pathological and clinical information was obtained with specific emphasis on the presence of a breast prosthesis. Logistic regression analysis was performed to estimate the relative risk of ALCL associated with breast prosthesis.

Results: 11 patients with ALCL of the breast were identified, diagnosed between 1994 and 2006 with a median age of 40 years (range 25-68 years). Of these, in 4 patients bilateral silicone breast prosthesis were placed 3, 4, 13 and 22 years prior to diagnosis all for cosmetic reasons. Of 48 potential controls, 12 patients were excluded for wrong diagnosis (no proven lymphoma, primary cutaneous lymphoma, relapse in the breast of primary nodal disease). 36 were considered eligible. Lymphoma classes were 15 diffuse large B-cell lymphomas, 5 Burkitt lymphomas, 8 MALT-type lymphoma, 5 follicular lymphomas and 3 peripheral T-cell lymphomas. One of 36 control patients had a breast implant, placed before diagnosis of lymphoma. This results in a relative risk for the development ofALCL associated with breast prosthesis of 20 (95% CI: 1.9-207).

Conclusion: This study suggests a strongly elevated risk for developing an ALCL in the breast in the context of silicone breast prostheses placed for cosmetic reasons.