

# T-cell lymphoma

## 229 EPSTEIN-BARR VIRUS DNA IN PERIPHERAL BLOOD AND EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE

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**Background:** Peripheral blood of patients with extranodal NK/T-cell lymphoma, nasal type (ENKL) contains fragmented Epstein-Barr virus (EBV) DNA. Measurement of the circulating viral DNA load has been reported to be useful for diagnosis, monitoring and prognostication of the disease. However, there are two different subjects for analysis, plasma and mononuclear cells (MNC). It remains unclear which are more useful target.

**Materials and Methods:** To evaluate clinical significance of peripheral blood EBV-DNA copy number for ENKL, we conducted a prospective study to analyze EBV-DNA with quantitative polymerase chain reaction. Primary endpoint was a prognostic value of EBV-DNA copy number to predict 2-year overall survival. Secondary endpoints were comparison of EBV-DNA copy number and pretreatment characteristics and prognostic capability of EBV-DNA during/after treatments. Three times of analysis, pre-treatment, mid-treatment, post-treatment, at central laboratory was to be performed for each patient. Interim analysis using pretreatment viral load, patient characteristics, and response to the first-line therapy is reported.

**Results:** From June 2004 to March 2007, 33 patients were registered. All patients were Japanese and diagnosed with ENKL. 21 were male and 12 were female. The median age was 56 years old, ranging from 18 to 81. There were 19 patients in stage IE, 3 stage IIE, 11 stage IV, respectively. 13 patients had B-symptom and 14 had elevated serum LDH level. ECOG performance status (PS) was 0 in 17 patients, 1 in 8, 2 in 4, 3 in 2, respectively. IPI was high-intermediate/high in 11. First line treatment included concurrent chemoradiotherapy in 16, radiotherapy followed by chemotherapy in 8, chemotherapy alone in 6. All but one patient were analyzed for peripheral blood EBV-DNA copy number before treatment. Pretreatment MNC and plasma EBV-DNA were detectable in 6 and 14 patients, respectively. The maximum copy numbers were 780 copies/ $\mu$ g DNA for MNC and 71000 copies/mL for plasma. Significant correlation was observed between mononuclear and plasma EBV-DNA copies ( $r=0.8741$ ,  $p<0.0001$ ). Plasma EBV-DNA well correlated with pretreatment clinical stage ( $p=0.02$ ), presence of B-symptom ( $p=0.02$ ), ECOG PS ( $p=0.02$ ), serum LDH level ( $p=0.05$ ), and soluble IL-2 receptor ( $p<0.0001$ ), but not with regional node involvement ( $p=0.17$ ), nasal vs. nasal-type ( $p=0.16$ ), and serum C-reactive protein ( $p=0.29$ ). Among 28 patients evaluable for response, 21 patients responded (CR/PR) to the first line treatment. Mean plasma EBV-DNA copy number before treatment was significantly higher in non-responders compared to responders (16472 copies/mL vs 2645 copies/mL,  $p=0.02$ ).

**Conclusions:** Our prospective study show pre-treatment EBV-DNA copy number in peripheral blood well correlate with clinical characteristics and response to the first-line therapy. Although plasma was more sensitive subject for analysis than MNC, clinical usefulness should be determined after examining prognostic significance.

## 230 CYTOKINE/CHEMOKINE EXPRESSION WITH PROTEIN ARRAYS IDENTIFIES THREE SUBSETS OF T-CELL LYMPHOMAS WITH DIFFERENT IMMUNOLOGICAL PROFILES

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**Background:** Only a few studies have addressed the expression of cytokine/chemokine in neoplastic T-cells related to the different histologic subtypes of T-cell lymphomas. The aim of this study was to analyze the cytokine/chemokine protein expression profiles and to correlate them with different histologic subtypes.

**Patients and methods:** Samples at diagnosis from 23 patients with T-cell lymphoma (unspecified peripheral T-cell lymphomas (uPTCL), 9 cases; angioimmunoblastic, 4; blastic T/NK, 2; panniculitis-like, 1; ALK-negative anaplastic large-cell (ALCL), 3; ALK-positive ALCL, 2; and lymphoblastic lymphoma (LL), 2) were studied by protein microarrays. In addition, one sample of a reactive lymphoid tissue was analyzed. Simultaneous detection of 174 cytokines was performed in three nitrocellulose membranes containing single band specific primary antibodies duplicated in array. Densitometry analysis was performed with Image Gauge software and an endogenous housekeeping gene was used to normalize results. Unsupervised clustering analysis was then performed.

**Results:** Three clusters were obtained. Cluster 1 included 4 nodal uPTCL and the 2 ALK-negative ALCL. The cytokine/chemokine profile was consistent with an activated Th1 pattern with high expression of CD62-L, CD25, CXCL16, CCL28, IL16, IL17, IL18

and IL21. Cluster 2 was composed by the 3 ALK-positive ALCL, 2 uPTCL and 4 different T-cell lymphomas, including angioimmunoblastic, panniculitis-like, blastic T/NK and LL (one each). This group exhibited a Th2 profile that was characterized by the expression of IL-10, MIG, MD, FGF-6 and TNF $\alpha$ . Finally, the analysis defined a cluster 3 constituted by 3 angioimmunoblastic, 3 uPTCL, 1 blastic T/NK and 1 LL. The cytokine/chemokine profile showed the expression of TIMP-1, TIMP2, GCSF, PIGF, ICAM3 and IGFBP3. The reactive lymphoid tissue clustered in the later group.

**Summary:** T-cell lymphomas show three different cytokine/chemokine patterns as determined by protein microarrays.

## 231 EXPRESSION OF NF-KAPPA B PATHWAY MOLECULES IN PERIPHERAL T-CELL LYMPHOMA NOT OTHERWISE SPECIFIED

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**Purpose:** Recent studies suggested differential expression of NF $\kappa$ B molecules among peripheral T-cell lymphomas (PTCLs), with possible prognostic relevance. We studied gene and protein expression of NF- $\kappa$ B related molecules in PTCL not otherwise specified (PTCL/NOS) in order to assess 1) the expression pattern of NF- $\kappa$ B among PTCLs/NOS, 2) the NF- $\kappa$ B cellular localization, and 3) the prognostic relevance of NF- $\kappa$ B expression.

**Experimental Design:** We studied by whole genome DNA-microarrays 28 cases of PTCL/NOS and 24 samples of normal T-cells and lymphoid tissues. Furthermore, we studied by immunohistochemistry the expression and cellular localization of RELA/p65, RELB/p50, and c-REL on tissue-microarrays containing 148 PTCL/NOS cases.

**Results:** First, we found differential expression of NF $\kappa$ B molecules in PTCL/NOS and normal T-lymphocytes. In particular, PTCL/NOS showed general down-regulation of RELA, RELB, and REL. Additionally, according to the expression of 109 NF $\kappa$ B related genes, PTCL/NOS could be divided into two main clusters (C1 and C2). Of note, cases included in PTCL/NOS C1 showed global down-regulation of NF $\kappa$ B pathway, while PTCLs/NOS C2 were characterized by the expression of several genes, but were clearly different from non-neoplastic samples. Secondly, we found that the vast majority of PTCL/NOS did express RELA, RELB, and c-REL at protein level. However, only few cases showed nuclear staining for such molecules, suggesting a non-active state of the system. Finally, we found that NF $\kappa$ B molecules expression did not significantly correlate with the clinical outcome.

**Conclusions:** PTCLs/NOS showed consistent de-regulation of NF $\kappa$ B pathway. Whether these abnormalities are determinant for PTCL/NOS pathogenesis should be defined in future studies.

## 232 GENETIC POLYMORPHISM AND PROTEIN EXPRESSION OF MOLECULAR MARKERS IN APOPTOTIC PATHWAYS IN T-CELL LYMPHOMA - A CORRELATIVE STUDY ON SUSCEPTIBILITY AND ANALYSIS OF CLINICAL FACTORS

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**Introduction:** T-cell lymphoma is a rare disease with unique biological behavior and largely elusive pathogenesis.

**Materials and methods:** Genotypes of CASP8 were determined by PCR-RFLP in 92 patients with T-cell lymphoma and 301 frequency-matched controls. The expression of Caspase-8AABCL-2 in 44 cases with peripheral T-cell lymphoma was examined with immunohistochemistry. The relationship between protein expression and clinical characteristics was analyzed.

**Results:** It was found that subjects with the CASP8 -652 6N ins/del genotype were at an increased risk for T-cell lymphoma (OR 1.93; 95% CI 1.13-3.31) compared with those with CASP8 -652 6N ins/ins genotype. It was observed that subjects having the -652 6N del/del genotype were at a 7.42-fold (95% CI 3.13-17.62) increased risk for T-cell lymphoma compared with those having the CASP8 -652 6N ins/ins genotype. We also investigated the association between genetic polymorphisms in CASP8 and B-cell lymphoma but no association was found. Cases with a negative or weak positive expression of Caspase-8 showed a higher frequency of B symptoms (10/25 vs 1/15,  $P=0.030$ ) and fever (7/25 vs 0/15,  $P=0.030$ ). BCL-2 expression was associated with a higher prognostic index for PTCL-U (8/10 vs 9/27,  $P=0.023$ ). Cases

with CASP8 -652 6N del/del genotype had a higher stage IV disease rate than those with ins/del or ins/ins (6/15 vs 5/52,  $P=0.008$ ). In patients with -652 6N del/del genotype, the positive rate of Caspase-8 was lower than in those with ins/del or ins/ins, with marginal significance ( $P=0.064$ ).

**Conclusions:** These data suggest that a six-nucleotide deletion (-652 6N del) variant in the CASP8 promoter is associated with increased risk of T-cell lymphoma, and CASP8 -652 6N del/del genotype and its functional change may have a role in the development of the disease.

### 233 CLINICO-PATHOLOGIC FEATURES AND OUTCOME OF 215 JAPANESE PATIENTS WITH T AND NK CELL NEOPLASMS

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**Background:** We studied the clinicopathologic features and treatment outcome of peripheral T-cell lymphoma (PTCL).

**Patients and methods:** A total of 1,545 patients with non-Hodgkin's lymphoma were treated in the ALTSG in Japan from 1998 to 2005. This study included 215 patients (13.9%) with T/NK-cell lymphoma, including 59 with PTCL-unspecified (PTCL-U), 42 with angioimmunoblastic T-cell lymphoma (AITL), and 20 with anaplastic large-cell lymphoma (ALCL).

**Results:** The patients with AITL and PTCL-U tended to be older than those with ALCL. AITL showed a male predominance. Stage III/IV disease was seen in 90.5% of the AITL cases, 55% of the ALCL cases, and 67.8% of the PTCL-U cases. In addition, 61.9% of the AITL cases had an IPI of H-I or H risk. Eighteen of the 20 ALCL patients, 40 of the 59 PTCL-U patients, and 25 of the 42 AITL patients achieved a complete response after their respective treatments. Among the patients with PTCL-U, the 5-year progression-free survival (PFS) in patients with L, L-I, H-I, or H risk according to the IPI, was 47.6%, 55.6%, 42.4% and 9.1%, respectively. Among the PTCL-U patients, the 5-year PFS according to the prognostic index of PTCL-U (PIT) in those in group 1, 2, 3 or 4 was 88.9%, 57.1%, 33.5%, or 13.3%, respectively. The 5-year OS among those in group 1, 2, 3, or 4 was 85.7%, 54.9%, 28.8%, and 13.3%, respectively. Next, the PFS and OS were examined according to the therapeutic method. The 5-year PFS among patients who received CHOP therapy, CycloBEAP therapy, or ASCT was 22%, 59%, and 33.3%, respectively. The 5-year OS among those who received CHOP therapy, CycloBEAP therapy, or auto-SIT was 25.7%, 61.7%, and 60%, respectively. Multivariate analysis revealed that the PIT score was associated with OS and PFS. These results indicate that the presence of bone marrow involvement is an independent prognostic factor which may predict both OS and PFS.

**Conclusion:** PTCL-U and AITL are diseases with relatively poor prognosis. However, PTCL-U is a heterogeneous disease with regard to histological type and pathological state. Because PTCL-U is generally not responsive to CHOP therapy, new treatment strategies need to be developed.

### 234 ARRAY CGH ANALYSIS OF NODAL T-CELL LYMPHOMAS: IDENTIFICATION OF GENOMIC ALTERATIONS SPECIFIC TO ANGIOIMMUNOBLASTIC AND UNSPECIFIED SUBTYPES, AND CORRELATION WITH GENE EXPRESSION SIGNATURE

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Genetic alterations underlying angioimmunoblastic and unspecified peripheral T-cell lymphomas (AITL and PTCL-u) are largely unknown.

Seventeen AITL and 16 PTCL-u previously characterized by gene expression profiling, were analyzed by CGH on DNA microarrays comprising 4434 BAC clones with a resolution of about 600 KB.

Chromosomal imbalances were identified in all cases. On average, more genomic alterations were detected in PTCL-u than in AITL ( $p=0.09$ ). PTCL-U cases had a mean of 302 aberrations (range, 55 to 892). Gains ( $n=668$ , 43 to 1810) were more frequent than losses ( $n=149$ , 3 to 1439). AITL cases also had more gains ( $n=520$ , 68 to 903) than losses ( $n=45$ , 13 to 1019). The most frequent recurrent gains, present in 50% of all cases, were observed at 1p36, 2q37, 4p16, 5p15, 6p12, 7p11;q36, 8q24, 9q34, 11p15, 11q13, 16p13; p33; q24, 17q12; q25, 19p13, 19q13; q33-q34, 20q11, 22q12, Xp11, Xq28. The only recurrent losses present in >50% of cases were at 1p21 and Yp11.3-q11.2. The comparison of the genomic profiles of AITL and PTCL-u identified 112 genomic alterations significantly associated with either type (Fisher test,  $p<0.05$ ). Several gains (at 1q, 5q, 6p, 7p, 12q, 13q, 17q) and losses at 14q were specifically associated with PTCL-u while gains at 10q and 15q and losses at 16p were associated with AITL. The coordinate analysis of the transcriptomic and CGH data identified 123 genes differentially expressed in PTCL-u and AITL mapping to genomic regions differentially altered ( $p<0.02$ ). Among these were 24 genes belonging to the molecular signature of these entities.

**In conclusion:** all nodal PTCL analyzed harbor genomic imbalances (gains>losses), of which many are common to AITL and PTCL-u; the pattern of genomic aberrations differs between the two groups, with certain aberrations being overrepresented in PTCL-u, and only a few specific for AITL; coordinate appraisal of transcriptomic and genomic data highlights correlations between genomic imbalances and gene expression signatures.

### 235 EXPRESSION OF CHEMOKINE RECEPTORS (CXCR3 AND CCR4) AND CYTOTOXIC MOLECULES IN PERIPHERAL T-CELL LYMPHOMA, UNSPECIFIED AND ALK-NEGATIVE ANAPLASTIC LARGE CELL LYMPHOMA

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**Background:** Peripheral T cell lymphoma unspecified (PTCL-U) and ALK-negative anaplastic large cell lymphoma (ALCL) are heterogeneous categories with poor diagnostic reproducibility.

**Methods:** Expression of two chemokine receptors, type 1 (Th1/Tc1)-associated CXCR3 and type 2 (Th2/Tc2)-associated CCR4, were examined in PTCL-U and ALK-negative ALCL cases, as well as the expression of cytotoxic molecules (CM). Subjects were 145 PTCL patients, comprising 110 cases of PTCL-U and 35 of ALK-negative ALCL. Immunohistochemical stainings for CXCR3, CCR4, TIA-1, and granzyme B were performed on 145 first diagnostic biopsy samples.

**Results:** CXCR3 and CCR4 were expressed in 69 (63%) and 37 (34%) of PTCL-U, and in 12 (34%) and 6 (17%) of ALK-negative ALCL, respectively. In PTCL-U, the type 1 pattern (CXCR3<sup>+</sup>CCR4<sup>-</sup>) was dominant (52%), whereas in ALK-negative ALCL, 54% were negative for both ( $P<0.0001$ ). CM was expressed in 38% of PTCL-U and 51% of ALK-negative ALCL. Most (86%) of CM-positive PTCL-U showed the type 1 phenotype, whereas none presented with the type 2 pattern (CXCR3<sup>+</sup>CCR4<sup>+</sup>). In contrast, CM-negative PTCL-U showed a heterogeneous pattern.

**Conclusion:** CM-positive PTCL-U is a distinct entity and should be differentiated from CM-negative PTCL-U.

### 236 BCL10 PROTEIN HIGHLY CORRELATES WITH THE EXPRESSION OF PHOSPHORYLATED-P65 NF-KB AND IT IS ASSOCIATED WITH THE CLINICAL OUTCOME OF PERIPHERAL T-CELL LYMPHOMA

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**Introduction:** Peripheral T-cell lymphomas (PTCL) are characterized by T-cell receptor (TCR) signaling alterations and NF-kB activation. Protein kinase C (PKC) is a family of proteins involved in signal transduction and mediates activation of the NF-kB pathway. In normal T cells, PKC  $\theta$  plays a major role in TCR-mediated activation of a novel NF-kB pathway that involves phosphorylation of p65 at Serine 536 (P-p65<sup>Ser536</sup>). BCL10 acts along the same pathway downstream of PKC  $\theta$  to activate NF-kB. We thus investigated the relationship between PKC  $\theta$ , BCL10 and P-p65<sup>Ser536</sup> status in biopsy specimens from patients with PTCL.

**Patients and Methods:** Paraffin-embedded tissues from 30 patients with nodal PTCL (PTCL unspecified, 21 cases; angioimmunoblastic, 3; ALK<sup>-</sup> anaplastic large-cell, 6) treated with curative intention were evaluated. Expression of PKC  $\theta$ , BCL10, and P-p65<sup>Ser536</sup> proteins were assessed using immunohistochemistry.

**Results:** Expression of PKC  $\theta$  was detected in 22 of 30 cases (73%), BCL10 in 20 of 30 (67%), and P-p65<sup>Ser536</sup> in 21 of 30 tumors (70%). BCL10 positive tumors were associated with PKC  $\theta$  (18 of 22) ( $P<0.0001$ ), and P-p65<sup>Ser536</sup> (19 of 21) expression ( $P<0.0001$ ). After a median follow-up of 60 months for surviving patients (range, 21-160 months), 5-year overall survival (OS) was 33%. Patients with BCL10 or P-p65<sup>Ser536</sup> positive tumors fared better, with a 5-year OS of 48% and 45%, respectively, versus 0% for those with negative tumors ( $P=0.029$ , and  $P=0.04$ , respectively). Remarkably, BCL10 expression identified a subgroup of patients within the low Ki-67 group (<80% positive tumor cells) with a different outcome; thus, within this subgroup patients with BCL10 positive tumors had a 5-year OS of 85% while it was 0% for those with BCL10 negative tumors ( $P=0.011$ ). Multivariate analysis showed that BCL10, Ki-67, and P-p65<sup>Ser536</sup> expression were independent factors associated with OS ( $P=0.039$ , 0.029, and 0.050, respectively).

**Conclusion:** BCL10 is expressed in PTCL, correlates with PKC  $\theta$  and P-p65<sup>Ser536</sup> NF-kB expression and it seems to be associated with better survival in PTCL.

### 237 COMPLETION OF PLANNED RADIOTHERAPY IS THE MOST IMPORTANT PROGNOSTIC FACTOR IN THE TREATMENT OF EARLY STAGE UPPER AERODIGESTIVE NASAL-TYPE NK/T CELL LYMPHOMA

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**Introduction:** This study reviews the role of radiotherapy (RT) for this rare lymphoma.

**Material & methods:** A retrospective review was conducted on 34 patients with stage I-II nasal NK/T-Cell lymphoma seen at our radiotherapy centre between 1996 and 2007.

**Results:** Nineteen had tumour involving sino-nasal complex only, 7 had involvement of the Waldeyer's ring and 8 had involvement at both sub-sites. Twenty-three had stage I, and 11 had stage II disease. Median follow-up was 35 months. Eight did not complete RT because of clinical deterioration or systemic progression while 2 because of severe acute radiation side effects. Median dose was 50 Gy in 1.8 – 2 Gy daily fractions using 6 MV photons. Twenty-five (73.5%) also had chemotherapy (CT). After commencement of CT, 5 required RT to be brought forward, due to disease progression (3) or severe side effects (2). Nineteen received early RT (after <4 cycles of CT) and 6 received late RT (after ≥4 cycles of CT). Median time from diagnosis to start of RT was 48 days.

Twenty-three (67.6%) had complete response, 7 (20.6%) had disease progression and 4 (11.8%) were not evaluable. Three-year disease-free survival (DFS) was 44%. The most important prognostic factors for DFS were presence of "B" symptoms ( $p=0.005$ ) and completion of planned radiotherapy ( $p<0.001$ ). Involvement of regional lymph node ( $p=0.083$ ) and stage II disease ( $p=0.083$ ) showed a trend towards inferior DFS. Treatment modality (RT alone or combination of CT and RT), and timing of RT were not significant in prognosticating DFS. In multivariate analysis, only the completion of RT was a significant prognostic factor (aHR =10.3; 95% CI 3.6 – 29.8). Three-year overall survival (OS) was 61%, with 13 deaths.

**Conclusions:** Our data showed that completion of RT plays a significant role in maintaining high DFS. RT remains a mainstay in the treatment for early stage disease. Novel systemic agents will need to be further evaluated to improve on the results.

### 238 HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL TRANSPLANTATION IN NASAL NK/T CELL LYMPHOMA: A RETROSPECTIVE COMPARISON WITH NON-TRANSPLANTATION CASES IN CHINA

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**Introduction:** Up to date, no standard therapy is clearly defined for Nasal NK/T cell lymphoma (NNTCL). To determine the role and indications of high-dose chemotherapy supported by autologous stem cell transplantation (HDC/ASCT) in Chinese NNTCL patients, a retrospective comparison was conducted in Tianjin Medical University Cancer Hospital, China.

**Material and methods:** Between 1992 and 2005, among 223 patients with newly diagnosed NNTCL, 22 eligible patients receiving HDC/ASCT were studied and 91 patients given conventional chemotherapy or radiotherapy were enrolled in the study as historical controls. They all achieved complete remission (CR) or partial remission (PR) after induction therapy, followed by HDC/ASCT or consolidation therapy.

**Result:** With a median follow-up of 30 months (range, 2 ~ 180 months), 9 (40.9%) of 22 patients relapsed after 3~61 months after HDC/ASCT. Among the 9 patients, 6 cases (27.3%) died of disease progression. Sixty-six patients (72.5%) given conventional therapy alone had a relapse and 54 patients (59.3%) died after relapsed. The median time from CR/PR to recurrence (range, 2-80 months) in patients received conventional therapy was shorter than that for transplantation (5 months vs. 16 months). A significantly better survival was demonstrated in patients who underwent HDC/ASCT as compared to those who did not (the estimated 5-year overall survival (OS) rates: 79.3% vs. 41.0%;  $P = 0.001$ ), as well as for patients with stage III E / IV E (the estimated 5-year OS rates: 70.0% vs. 15.2%,  $P=0.000$ ) and those with stage II E (the estimated 5-year OS rate 88.9% vs. 44.0%,  $P=0.013$ ). Moreover, in subset analysis, the stage II E patients who were received conventional therapy with B symptom and IPI score ≥2 had a significantly inferior survival compared to those without B symptom (the estimated 5-year OS rates: 25.7% vs. 50.0%,  $P = 0.003$ ) and IPI score <2 (the estimated 5-year OS rates: 21.2% vs. 54.6%,  $P = 0.032$ ). In non-HDC/ASCT group, patients with stage I E also had better survival outcome than those with stage II E ( $P = 0.011$ ).

**Conclusions:** HDC/ASCT should be recommended as a highly effective primary therapy for patients with previously untreated NNTCL, especially for those with advanced disease (stage III/IV) in CR or PR status through induction therapy and with stage II and high risk prognostic factors such as B symptom and high IPI score.

### 239 AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN EXTRANODAL NK/T CELL LYMPHOMA: A MULTINATIONAL, MULTICENTER, MATCHED CONTROLLED STUDY

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This retrospective analysis studied the potential survival benefits of HSCT in comparison with a historical control group. 47 patients from 3 previously published series of HSCT were matched according to NK-IPI risk groups (risk score 0,1 vs 2 – 4) and disease status at transplantation with 107 patients from a historical control group for analysis. After a median follow-up duration of 116.5 months, the median survival time has not been reached for the HSCT group while it was 43.5 months for the control group (95% CI, 6.7 – 80.3,  $P=127$ ). In patients who were in CR at the time of HSCT or of surveillance following remission, disease-specific survival rates were significantly higher in the HSCT group as compared with the control group (5-year survival rate, 87.3% vs 67.8%,  $P=027$ ). In patients in non-CR, there were no significant difference between the HSCT and the control group ( $P=141$ ). The impact of HSCT on survival of all patients was significantly retained at multivariate level with 2.1-fold (95% CI, 1.2 – 3.7) reduced risk of death ( $P=006$ ). HSCT seems to confer survival benefit in pts who attained CR as post-remission consolidation therapy, especially in pts with high NKIPI risk scores.

### 240 THE CLINICAL OUTCOME OF AUTOLOGOUS STEM CELL TRANSPLANTATION IN PATIENTS WITH PERIPHERAL T CELL LYMPHOMA UNSPECIFIED

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High-dose chemotherapy followed by autologous stem cell transplantation (HDT/ASCT) has represented a rescue option from poor prognosis.

**Patients and Methods:** We retrospectively investigated the clinical outcome of HDT/ASCT in 64 Korean patients with peripheral T cell lymphoma unspecified (PTCL-U) between March 1995 and Feb. 2007.

**Results:** The median age at transplantation was 41 years (15-68). 28 patients presented with high risk group according to age-adjusted IPI (a-IPI) and 16 patients were classified into poor risk group by prognostic index for PTCL (PIT) 2-3 at diagnosis. After a median follow-up of 29.7 months, the 3-year probability of overall survival (OS) and progression-free survival (PFS) was 53.0 ± 7.5% and 44.3 ± 7.0%, respectively. According to univariate analysis, poor performance status (PS), high LDH, high a-IPI, high PIT, failing to achieve CR at transplant and non-frontline transplantation were associated with a poor OS. Moreover, LDH, a-IPI and a-PIT showed significant prognostic differences for PFS. In multivariate analysis, the achievement of CR at transplant and high PIT (2-3) were independent prognostic

factors for OS with a hazard ratio (HR) of 2.23 (1.78–7.93) and 3.76 (1.02–5.42), respectively.

**Conclusion:** The a-IPI and PIT showed high differentiation potency in predicting the prognosis of HDT/ASCT. The achievement of CR at transplant and PIT predict the outcome after ASCT in patients with PTCL-U.

#### 240 bis ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT) AFTER NON-MYELOABLATIVE CONDITIONING FOR RELAPSED AND REFRACTORY T / NK-CELL LYMPHOMAS

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**Background:** Patients with relapsed/refractory T/NK-cell lymphomas have poor outcomes with few therapeutic options. Some patients with chemo-sensitive disease can be salvaged with autologous HCT. Allogeneic HCT with myeloablative conditioning can be offered to younger patients but treatment related mortality is high. We examined the outcomes of allogeneic HCT after non-myeloablative conditioning in this setting.

**Patients and Methods:** In this multi-institutional phase II trial fifteen patients received salvage therapy followed by conditioning with 2 Gy of total body irradiation and fludarabine, (30mg/m<sup>2</sup> X 3 doses) followed by HCT from HLA-matched related (n=5) or unrelated (n=10) donor. Graft-vs-host disease (GVHD) prophylaxis consisted of cyclosporine and mycophenolate mofetil. Three patients had precursor T-cell neoplasm, 1 had blastic NK-lymphoma and 11 patients had various histologies of peripheral T-cell lymphomas. Median age of patients was 57 (range, 18 to 72) years and median number of prior therapies was 4, including prior autologous SCT in 7. Four patients had progressive disease.

**Results:** Seven of the 15 patients are alive in CR with a median follow-up of 3.0 (range, 1.5 to 5.0) years. Five patients died from progressive disease, one died of GVHD and 2 died of other treatment related causes. Estimated 3-year overall and progression-free survivals were 47%. The incidence of acute GVHD, grade 3 and 4 acute GVHD and extensive chronic GVHD were 73%, 33% and 60%, respectively. The estimated probabilities of 3-year non-relapse and relapse mortalities were 20% and 33%, respectively.

**Conclusions:** Allogeneic HCT after non-myeloablative conditioning is a promising salvage option for patients with relapsed/ refractory T/NK-cell lymphomas, has acceptable treatment-related mortality and extends the conventional age limitations for this approach. Results suggest that graft-versus-T-cell lymphoma activity is responsible for long-term disease control.

#### 241 PHASE II OPEN-LABEL TRIAL OF BELINOSTAT (PXD101) IN PATIENTS WITH RECURRENT OR REFRACTORY PERIPHERAL OR CUTANEOUS T-CELL LYMPHOMA

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**Background:** Belinostat is a hydroxamate pan-HDAC inhibitor with broad preclinical anti-cancer activity that is well-tolerated and has shown activity in the clinic.

**Methods:** Global, open-label, multicenter Ph II trial that enrolled patients (pts) with peripheral T-cell lymphoma (PTCL) or cutaneous T-cell lymphoma (CTCL) who failed  $\geq 1$  prior systemic therapy. Pts received 1000 mg/m<sup>2</sup> IV belinostat over 30-min days 1-5 of a 3-wk cycle. Primary endpoint was objective response (OR) assessed by IWG criteria for PTCL or by SWAT for CTCL. For each study group a Simon 2-stage design was used with 25% target OR rate.

**Results:** PTCL group-14 pts (7 PTCL-unspecified (PTCL-U), 3 anaplastic large cell lymphoma (ALCL), 2 angioimmunoblastic TCL, 1 NK-TCL, 1 subcutaneous panniculitis-like TCL (SPTCL)) were treated for a median of 2.5 cycles (range 1-6). Of 10 evaluable pts, 2 CR (duration 18+ and 21+ wks) both in pts with PTCL-U and 4 SD (median duration 14 wks, range 12-23) in pts with PTCL-U, ALCL, and NK-TCL, were observed. Two pts are ongoing. CTCL group-21 pts (11 mycosis fungoides (MF), 7 Sezary syndrome (SS), 2 primary cutaneous ALCL, 1 SPTCL), 67% at Stage IV, were treated for a median of 2 cycles (range 1-6). 3 ORS in 19 evaluable pts: 1 CR (ALCL) and 2 PR (1 MF/1 SS). Median OR duration was 17 wks (range 7-55+ wks). 13/18 pts (72%) with evaluable scores had a decrease in SWAT. 6/7 pts with significant pruritus had improvement. Most common (>10%) drug-related adverse events (AE) were nausea, vomiting, injection site reaction, flushing, and anorexia. Grade 3/4 drug-

related AE reported in 6 pts were rash, adynamic ileus, apraxia, infection, peripheral edema, pneumonitis, pruritus, and thrombocytopenia.

**Conclusions:** The OR rate in both groups met the criteria for expansion and is accruing 34 pts per group. Belinostat appears well-tolerated and shows clinical activity in PTCL and CTCL.

#### 242 CLINICAL EFFICACY AND SAFETY OF VORINOSTAT IN RELAPSED/ REFRACTORY CTCL

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**Background:** Vorinostat (Zolinza™) is an orally active, potent inhibitor of histone deacetylase. Here we report corroborative conclusions on the clinical efficacy of vorinostat in cutaneous T-cell lymphoma (CTCL) based on the results from two completed Phase II studies.

**Materials and methods:** An initial study exploring various vorinostat dosing regimens and a second pivotal study using a 400 mg qd dose, enrolled patients (pts) with advanced CTCL who were refractory to and/or intolerant of other therapies. Pts in the initial study must have received  $\geq 1$  prior systemic therapy for CTCL compared with  $\geq 2$  in the pivotal study. Only those pts in the initial study that were treated with vorinostat 400 mg qd (the FDA-approved dose in CTCL) are included in the comparison. The primary endpoint in both studies was objective response rate (ORR).

**Results:** The two studies were similar with respect to baseline characteristics. A total of 87 pts were included in the combined analysis. At baseline, 72 had  $\geq$  Stage IIB CTCL. ORRs were comparable between the pts taken from the initial study and the pivotal study overall (30.8% and 29.7%, respectively) and in pts with Stage IIB or higher (36.4% and 29.5%, respectively). Median time to objective response ranged from approximately 2 to 3 months; 88 days and 55 days in the initial and pivotal studies, respectively. Median duration of response (DOR) was 113 days in the initial study versus in excess of 4 months (upper range: 322 days) in the pivotal study (DOR not reached, study ongoing for duration). Of particular interest was the clinically meaningful reduction in pruritus in symptomatic pts in both studies; 72.7% in the initial study and 31.9% in the pivotal study reported pruritus relief. Furthermore, complete resolution of pruritus was observed in 9.1% and 11.1% of pts, respectively. Vorinostat was associated with an acceptable safety profile and was generally well tolerated in both studies.

**Conclusions:** Even though required prior treatment and evaluation of response differed, response rates were similar and clinically meaningful in a substantial proportion of pts with CTCL (Stage IB and above), who had progressive, persistent, or recurrent disease subsequent to prior therapies.

#### 243 L-ASPARAGINASE IN THE TREATMENT OF EXTRA NODAL NK/ T-CELL LYMPHOMA

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**Background:** Extra nodal NK/T-cell lymphoma, nasal type, is an EBV-related highly aggressive disease with a poor outcome, especially when disseminated or recurrent. L-Asparaginase seems to have a particular efficacy in this disease.

**Material and methods:** We used this drug in 12 French centers to treat 27 patients with relapsed, refractory or disseminated nasal type NK-T-cell lymphoma. Fifteen patients were retrospectively collected and twelve patients were treated in a prospective phase II trial using L-asparaginase (Kidrolase®) 6000 U/m<sup>2</sup> IM at day 2, 4, 6, 8, methotrexate 3 gr/m<sup>2</sup> at day 1 and dexamethasone 40 mg at day 1 to 4 with 3 weeks cycles.

**Results:** There were 20 men and 7 women, median age was 55 (38 to 81), 13 were primary refractory, 12 were in relapse, 15 were in stage IV including the 2 patients treated upfront. L-asparaginase, 6000 U/m<sup>2</sup> (1 to 6 courses) was given for 4 to 10 days associated with Dexamethasone 40 mg for 4 days (n=23), methotrexate 3 gr/m<sup>2</sup> (n=16) or velbe 6 mg (n=1). Six patients who had a severe anaphylactic reaction with L-asparaginase received further courses of Erwinase® (n=3) or PEG-asparaginase (Oncaspar®) (n=3). Treatment efficacy was evident in all patients but three, 12 patients were in documented complete remission (CR) after treatment with L-asparaginase. Fourteen patients died of unrelated causes (n=5) or progression of disease (n=9). Toxicity related to L-asparaginase was mild, mainly brief leucopenia and elevation of alanine aminotransferase. Thirteen patients are still alive with a median follow-up of 14 months (1 to 49), 9 patients are in persistent CR, 3 had received high dose therapy with autologous stem cell transplant and 2 patients received irradiation after L-asparaginase treatment.

**Conclusion:** The efficacy of L-asparaginase to treat extra nodal NK-T-cell lymphoma must be known because of the very poor prognosis of patients with disseminated or

relapsing disease with conventional chemotherapy. Prospective studies using L-asparaginase for de novo patients are warranted.

#### 244 CLOFARABINE IS ACTIVE IN PERIPHERAL T-CELL LYMPHOMAS: RESULTS OF THE PHASE I PORTION OF A PHASE I/II STUDY

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**Background:** Clofarabine is a nucleoside analog with increased stability and prolonged intracellular half-life. Clofarabine leads to cell death through 1) Inhibition of ribonucleotide reductase 2) inhibition of chain elongation by DNA polymerases 3) disruption of mitochondrial membranes. In trials for acute leukemia, several complete responses (CR) were seen among patients (pts) with T or NK lymphoma (TCL). To explore this activity we are conducting a phase I/II trial in TCL.

**Methods:** The phase I part of this study used an accelerated titration design-starting at 4 mg/m<sup>2</sup> daily for 3 consecutive days. Cycles are repeated q 3 weeks (max 8). Upon

grade 2 non-heme toxicity, the dose escalation is switched to a traditional 3-6 pts / cohort design. Eligibility required a diagnosis of rel/ref TCL without standard curative options; relapse post autologous or allogeneic stem cell transplantation is permitted.

**Results:** To date, 11 pts have enrolled on the phase I. Histologies include: PTCL 2, HTLV-1-lymphoma 2, Alk-1 negative Anaplastic Large Cell lymphoma 2, NK or NK/TCL (NK/T) 2, Angioimmunoblastic TCL (AITL) 1, Lymphoblastic lymphoma 1, Transformed mycosis fungoides 1.9 pts were refractory to their last therapy. Cohorts were: 4 mg/m<sup>2</sup> n=1, 8 mg/m<sup>2</sup> n=3, 13.2 mg/m<sup>2</sup> n=3, 20 mg/m<sup>2</sup> n=3, 28 mg/m<sup>2</sup> n=1. Grade (Gr) 3-4 heme tox were neutropenia n=6, thrombocytopenia n=6, anemia n=5. Gr 3-4 drug related non-heme tox were fever and neutropenia n=2. All toxicities except thrombocytopenia in 1 pt (28 mg/m<sup>2</sup>) resolved to allow the next cycle with ≤ 1 week delay. Best responses were SD 5, PR 1, CR 1.4 pts had primary progression. CR was seen in 1 pt with AITL at 8 mg/m<sup>2</sup>. This pt remains in CR >9 months from end of therapy. 1 pt with NK/T had a PR after 6 cycles at 13.2 mg/m<sup>2</sup>. 2 pts with SD remain on treatment.

**Conclusions:** In this Phase I/II study, Clofarabine showed activity, including a durable CR at doses much lower than used for acute leukemia. The phase I portion continues accrual with an expansion at the MTD. This treatment has been very well tolerated in heavily pre-treated pts. DLTs have not been seen. This activity at well tolerated doses suggests a role for clofarabine in managing TCL and may be a good candidate for combination regimens.