T-cell lymphoma

240 IMPROVED PROGNOSIS OF NK-CELL LYMPHOMA/LEUKEMIA, BUT NOT FOR T-CELL LYMPHOMAS: A NATIONWIDE SURVEY OF NK- AND ASSOCIATED T-CELL NEOPLASMS BY THE NK-CELL TUMOR STUDY GROUP (NKTSG)

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Purpose: To explore the clinicopathologic features of NK- and related T-cell lymphomas, a nationwide survey was conducted.

Methods: A questionnaire was sent to 99 institutions. ALCL,AITL, and non-cytotoxic nodal PTCL-NOS were not included.

Results: A total of 969 patient data (M:F=621:348) were collected. The median age was 53 years (range: 1-91). 343 pts were diagnosed with NK-cell tumor, and 417 with T-cell lymphoma, but 9 remained unclassifiable. These included 413 with extranodal NK/T cell lymphoma (ENKL) and 46 with aggressive NK-cell leukemia. Among T-cell lymphoma, included were 23 with enteropathy-associated T-cell lymphoma, 25 with hepatosplenic T-cell lymphoma, 6 with gamma-delta T-cell lymphoma, and 196 with PTCL-NOS. 285 received stem cell transplantation. 5y-overall survival (5yOS) for localized and advanced NK-cell malignancy was 57% and 16%, respectively. In contrast, the 5yOS was almost the same for T-cell lymphomas (46% vs. 49%).

Conclusion: Although the prognosis of NK- and T-cell neoplasms is poor, the former is improving by adopting new treatment regimens. Further investigation is required to improve the prognosis of T-cell lymphoma.

Table. Changing trends of treatment for NK- and T-cell malignancies.

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<tr>
<td>CHOP</td>
<td>53%</td>
<td>29%</td>
<td>16%</td>
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<td>3rd gen.</td>
<td>36%</td>
<td>19%</td>
<td>12%</td>
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<td>DevIC</td>
<td>3%</td>
<td>43%</td>
<td>59%</td>
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<tr>
<td>SMILE</td>
<td>0%</td>
<td>2%</td>
<td>11%</td>
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<tr>
<td>CR rate</td>
<td>42%</td>
<td>56%</td>
<td>68%</td>
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<tr>
<td>3yOS</td>
<td>34%</td>
<td>45%</td>
<td>49%</td>
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<tr>
<th>N=56</th>
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<tr>
<td>CHOP</td>
<td>78%</td>
<td>78%</td>
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<tr>
<td>3rd gen.</td>
<td>13%</td>
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<tr>
<td>Others</td>
<td>9%</td>
<td>6%</td>
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<tr>
<td>CR rate</td>
<td>51%</td>
<td>39%</td>
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<tr>
<td>3yOS</td>
<td>47%</td>
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241 T-CELL PROJECT: AN INTERNATIONAL, PROSPECTIVE, OBSERVATIONAL STUDY OF PATIENTS WITH AGGRESSIVE PERIPHERAL T-CELL LYMPHOMA. ANALYSIS OF FIRST 524 PATIENTS.


Background: Recently, the prognosis of Follicular Lymphoma has been investigated by means of prospective international collection of data, allowing to analyze cases diagnosed in a short time. Similarly, the T-Cell Project has been designed as a prospective registry devised for investigating the prognosis of aggressive PTCLs.

Methods: The purpose is to verify if a prospective collection would allow to achieve more accurate data to better define prognosis of PTCLs. Eligible pts with naive PTCL are registered at a website via secure HTTP protocols, and followed for up to 5 years.

Results: Between Sept 2006 and Jan 2011, 701 cases from 61 European, North/South American and Asian Institutions were registered. The Table below summarizes characteristics of pts entered on Dec 2009 (N=524). Data on treatment were available in 426 pts (94%) were delivered therapy with curative intent. After a mean follow-up of 13 mos (1-49), 152 pts died (29%), mostly from lymphoma (74%), with a 3-y OS of 43%.

Conclusions: The T-Cell project confirms that a web based world-wide cooperation allows to collect a relevant and quite complete set of data in a short time; it also represents a virtual bio-bank for future pathobiological studies to identify novel therapeutic targets.

Baseline Characteristic [524] %

| Male gender | 63 |
| Age > 60 yrs | 39 |
| Mean (Range) | 54 (17-89) |
| Hystology | 52 |
| PTCL - NOS | 37 |
| AITL | 16 |
| ALCL, ALK- | 15 |
| ALCL, ALK+ | 6 |
| Hepatosplenic | 2 |
| Enteropathy type | 3 |
| NKTCL | 13 |
| Subcutaneous panniculosis like | 3 |
| Peripheral | 2 |
| Other subtypes | 5 |
| ECOG > 1 | 26 |
| B symptom | 50 |
| Other symptom | 70 |
| Stage III-IV | 70 |
| Disease type | 83 |
| Nodal | 28 |
| Extranodal | 25 |
| Both N+E | 47 |

242 COMPREHENSIVE ONCOLOGY MEASURES FOR PERIPHERAL T-CELL LYMPHOMA TREATMENT (COMPLETE), A NEW INTERNATIONAL TREATMENT REGISTRY


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Background: Registries can be invaluable for describing patterns of care and providing data on a population of patients (pts). We report initial findings from COMPLETE, a new international registry of peripheral T-cell lymphoma (PTCL) pts.

Methods: This is a prospective, multinational, longitudinal, observational registry led by a global steering committee. Pts with newly diagnosed PTCL and providing written informed consent are eligible. Pts are entered in the registry from initial diagnosis and followed for ≤5 years.

Results: The first patient was enrolled from the US on 5 Feb 2010. A total of 48 pts have been enrolled to date from 21 US academic and community sites. Pts from Europe are expected to be enrolled beginning in Apr 2011. Baseline characteristics can be found below.

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Baseline Characteristic | N | Percent
--- | --- | ---
Gender | 48 | 
Male/Female | 27 / 21 | 56% / 44%
Age (years) | 48 | 
Mean (Range) | 57 (22-95)
Histology | 43 | 
PTCL - not otherwise specified | 16 | 37%
Anaplastic large T-cell lymphoma | 9 | 21%
Hepatosplenic T-cell lymphoma | 2 | 5%
Transformed mycosis fungoides | 2 | 5%
T/NK-cell lymphoma, nasal | 2 | 5%
Other | 3 | 7%
B symptoms | 44 | 
Yes | 22 | 50%
Ann Arbor stage | 39 | 
I, II | 8 | 21%
III, IV | 31 | 79%
Sites of disease | 41 | 
Nodal only | 19 | 46%
Extranodal only | 13 | 32%
Nodal and extranodal | 9 | 22%

Limited treatment (tx) data are available. Tx intent was palliation and cure in 19% and 81% of pts, respectively. Most common factors influencing tx choice were presence of disseminated disease, PTCL sub-type, and data from literature. Details on tx will be available at time of presentation.

**Conclusions:** COMPLETE is a new international initiative that will further the understanding of the care of PTCL pts.

### 243 POORER PROGNOSIS OF MATURE T/NK CELL LYMPHOMA IS MAINLY DUE TO THE DIFFERENCE IN THE CLINICAL OUTCOME OF IPI LOW RISK GROUP WHEN COMPARED WITH DIFFUSE LARGE B CELL LYMPHOMA


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**Introduction:** Mature T/NK cell lymphoma shows the poorer prognosis than aggressive B cell lymphoma even in pre-rituximab era. T cell phenotype has been indicated as a significant prognostic factor especially by the cohort study of well designed clinical trials. We conducted a retrospective cohort study to compare the clinical outcomes between T/NK cell lymphoma and aggressive B cell lymphoma and to elucidate the impact of IPI in T/NK cell lymphoma in actual clinical practice.

**Materials and Methods:** This was a retrospective cohort study that examined the clinical outcome of all untreated patients with B and T cell lymphoma who visited 20 hospitals of the National Hospital Organization from January 2000 to December 2004. HTLV-1 positive adult T-cell lymphoma was excluded. PFS and OS were assessed using the Kaplan-Meier method, and the groups were compared using the log-rank test.

**Results:** A total of 1394 patients were newly diagnosed non-Hodgkin lymphoma during this study period. Among them, 165 patients (12%) were diagnosed as mature T/NK cell lymphoma. The most common subtype was PTCL-NOS (n=57, 35%). Forty three AILTs (26%), 26 ALCs (16%), and 25 extranodal NK/T cell lymphomas (15%) were included. The CTCL case was 4. Six hundred twelve DLBCLs treated without rituximab as first remission induction (pre-rituximab DLBCL) were also enrolled. 3 yrs OS was 64.8% in IPI low risk, 51.7% in IPI intermediate risk (low-intermediate and high-intermediate), and 31.5% in IPI high risk, therefore IPI could predict survival of mature T/NK cell lymphoma. Malignant T/NK cell lymphoma consisted of higher proportion of IPI higher risk patients than DLBCL. As shown other studies, the survival rate of T/NK cell lymphoma showed poorer tendency than pre-rituximab DLBCL. When subgrouping according to IPI, OS of intermediate and high risk patients were not significantly different between mature T/NK cell lymphoma and pre-rituximab DLBCL (P=0.42 and 0.18), but low risk T cell lymphoma showed significantly worse survival than pre-rituximab DLBCL (3 yrs OS 86% vs. 65%, P<0.001).

**Conclusion:** This retrospective study indicated the good predictive value of IPI system when stratifying into low, intermediate (low-intermediate/high-intermediate), and high risk group in mature T/NK cell lymphoma in clinical practice. Poorer prognosis of mature T/NK cell lymphoma might be explained by the higher proportion of IPI higher risk patients and the difference in the clinical outcome of IPI low risk group compared with pre-rituximab.

### 244 CHROMOSOMAL ABERRATIONS IN PERIPHERAL T-CELL LYMPHOMA, NOT OTHERWISE SPECIFIED, ARE SIGNIFICANTLY ASSOCIATED TO POOR PROGNOSIS

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**Introduction/Background:** Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), comprises a heterogeneous group of haematological neoplasms originated from mature T-cells. Despite the recent advances in our understanding of the biology and genetics of PTCL-NOS, the molecular mechanism underlying its pathogenesis is still not fully understood.

**Patients and Methods:** A total of 31 cases of PTCL-NOS were investigated by immunophenotyping, clonality analysis and 1Mb resolution array comparative genomic hybridisation (Array-CGH).

**Results:** In general, there was a considerable overlap in the CGH profiles among the PTCL-NOS cases studied. The regions with most recurrent genomic gains (≥4 cases) were 1p36.13-1p36.32, 7q22.1, 7q36.1-7q36.3, 7q32.1-7q32.3, 7q22.1-7q34, 9p11.2-9q12 and 9q53.3-9q54.3. The regions with most recurrent genomic losses were 1p12-1p21.1 and 13q14.11-13q14.3. Follow-up study showed that the patients with more dramatic copy number changes (≥6 regions/case) had shorter survival time than those without (follow-up data available in 25 cases, time range 3-32 months, died in 20 cases and alive in 5 cases; P<0.05), and chromosomal alterations, i.e., gain or loss in 1p56.13-12, losses in 1q, 12p13.1-2, 13q14.1-11, 13q21.3-22, were also significantly related with poor prognosis (P<0.05).

**Conclusions:** Genomic gains and losses are frequently seen in PTCL-NOS using array-CGH and patients with multiple chromosomal alterations (≥6 regions) have poor prognosis. The genomic profiling is therefore useful to identify a distinct subgroup of PTCL-NOS with adverse clinical course.

### 245 RITUXIMAB IN COMBINATION WITH CHOP REGIMEN IN ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA (AILT): CLINICAL AND BIOLOGICAL RESULTS OF A PROSPECTIVE PHASE II STUDY OF THE GROUPE D'ETUDE DES LYMPHOMES DE L'ADULTE (GELA)


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**Background:** AILT is of poor prognosis. The tumor cells are derived from follicular Helper T Cells, a cell subset normally involved in the selection of Germinal Center B cells. AILT encompasses manifestations of B-cell hyperstimulation, and involved tissues comprise CD20+ B-blasts, suggesting that functional B-T interactions still persist in the tumor. Whether the presence of EBV infected cells is involved in tumor development or reflects immune deregulation, is under debate. We postulated that the disruption of T-B interactions and/or EBV reservoir depletion by rituximab could suppress survival signals and add to the apoptotic CHOP chemotherapy.

**Methods:** 25 patients (pts) with newly diagnosed AILT were treated with 8 cycles of R-CHOP1. Tumor cell, B blast, EBV-positive cell densities were scored (1-low to 3-high) on diagnostic biopsies. Peripheral Blood lymphocytes and circulating tumor cells (pan-T antigen loss and/or CD10 coexpression) were counted by flow cytometry. Lymphocyte clonality and EBV DNA quantification were performed on DNA extracted from frozen biopsies and PBMC when available.

**Results:** Median age was 67 y. Most of the pts had an advanced disease (stage IV: 88% and B symptoms 60%). The ORR was 92%, 44% achieving CR. The 2y-Progression Free Survival and OS were 44% and 62%. Biopies were scored 3 for tumor load in 9/25 pts and for B blasts in 9/25 pts. EBV was detected in 24/25 tumors by SISH and in 14/21 PBMC by QPCR. The abundance of EBV DNA in PBMC correlated with EBV scoring in tissues (p<0.004). Lymphopenia <700 CD3/mm3 was found in 12/21 pts without correlation to circulating EBV quantification. Circulating tumoral cells were detected in 12/21 pts (57%), a feature associated with poorer response to treatment (p=0.06). EBV viral load in PBMC > 100 copies/μl tended to be associated with shorter PFS (p = 0.06).

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Conclusion: R-CHOP21 was well tolerated in elderly pts withAITL but did not improve the CR rate from CHOP alone. Intriguing results are the relationship between circulating EBV and prognosis, independently of T-lymphoma, but in relationship with circulating tumoral cells.

246 ALLOGENEIC STEM CELL TRANSLANTATION FOLLOWING A REDUCED INTENSITY CONDITIONING REGIMEN IN RELAPSED PERIPHERAL T-CELL LYMPHOMAS (PTCL): RESULTS AFTER A MEDIAN FOLLOW-UP OF 67 MONTHS

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Introduction: Allogeneic stem cell transplantation give disappointing results in relapsed peripheral T-cell lymphomas (PTCL). In a observational retrospective study, we have evaluated the outcome of 52 patients (pts) receiving allogeneic stem cell transplantation (alloSCT) for relapsed disease.

Material and Methods: Histopathological subtypes were PTCL-not otherwise specified (n=23), anaplastic large-cell lymphoma (n=11), and angioimmunoblastic T-cell lymphomas (n=9) and rare subtypes (n=9). All pts received a reduced-intensity conditioning regimen. Pts were alloagrafted from matched related siblings (n=34), 65% or alternative donors (n=18, 35%). Most of the pts had chemotherapy-sensitive disease (n=39, 75%). Twenty-seven (52%) had a previous diagnose of extranodal disease and ten pts (19%) had bone marrow involvement.

Results: At the last follow-up (median 67 months, range 18-138), 27 pts are alive (52%) and 25 (48%) had died: n=19 disease progression, n=6 non-relapse mortality (NRM). The crude cumulative incidence (CCI) of NRM at 5 years was 12%. Extensive chronic GVHD increased the risk of NRM (33% versus 8%, p=0.04). The CCI of relapse was 49% at 5 years: pts heavily pretreated had a higher risk of relapse (72% versus 36%, p=0.007). Five years OS and PFS were 50% (95% CI, 36% to 63%) and 40% (95% CI, 27% to 53%). Among different subtypes, we did not observe a difference in outcome. Bone marrow involvement or extranodal disease did not influence PFS or OS. At multivariable analysis of OS and PFS, refractory disease prior to alloSCT and age over 45 years were independent adverse prognostic factors [hazard ratio (HR)=5 (p=0.002), HR=6.9 (p=0.001) for OS, HR=5 (p=0.003), HR=5.1 (p=0.01) for PFS].

Conclusions: The long-term observation period showed that an immunological control of lymphoma occurred following RIC alloSCT.

247 DENILEUKIN DIFITIXO FOR THE TREATMENT OF CD25 LOW EXPRESSION CUTANEOUS T-CELL LYMPHOMA

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Introduction: Denileukin difitixio (DD; ONTAK®) therapy for persistent or recurrent cutaneous T-cell lymphoma (CTCL) targets malignant T-cells based on IL-2 receptor (IL-2R) expression: low (CD25), intermediate (CD122/CD132), or high (CD25/ CD122/CD132) binding affinity. A screening assay identifies patients (pts) who may respond to DD based on CD25 expression; however, CD25 is not expressed on the IL-2R intermediate affinity isoform, an arbitrary value of ≤20% is defined as positive, and CD25 assay techniques are inconsistent.

Methods: We examined pts excluded from the L4389-11 phase III trial because of low CD25 expression. These pts received DD 18 mg/kg/iv every 3 weeks for 5 cycles. No changes in dose were made during the study. Results: Of the 52 pts, 36 had CD25 low expression, 15 had CD25 intermediate expression, and 1 pt had CD25 high expression. The protocol response was objective response (OR) in 1 pt (3%) with a partial response (PR) in 2pts (6%). The median time to response (TTR) was 3.5 months (range: 1.2-57) months.

Conclusions: Denileukin difitixio has high activity in CD25 low expression CTCL. These results are consistent with the results from L4389-11 study. Long-term follow-up is necessary to determine the durability of response.

248 COMPLETE REMISSION OF REFRACTORY ALCL BY INHIBITION OF THE PDGF-RECEPTOR WITH IMATINIB

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Anaplastic large-cell lymphomas (ALCLs) are non Hodgkin Lymphomas of T-cell origin, comprising 40% of all non-Hodgkin Lymphomas of childhood and 2%-8% of adulthood. Half of the cases are associated with a t(2;5) translocation, leading to the fusion of NPM gene and ALK tyrosine kinase, resulting in its constitutive activation. ALK+ ALCLs usually have a favourable outcome with a good response to CHOP-chemotherapy. Relapses occur in 30%, but are usually responsive to autologous stem cell transplantation. Imatinib is a tyrosine kinase inhibitor with high affinity to inhibition of BCR/ABL, ckit and PDGFR tyrosine kinases. We report on a patient with ALK+ALCL, diagnosed in March 2010, clinical stage IIIb, IPI 1, who had an early relapse after 8 cycles of CHOP two month after the end of induction therapy. He was subsequently treated with ICE chemotherapy in September 2010 and underwent autologous stem cell transplantation in November 2010. Four weeks after ASCT the patient relapsed again indicating refractory ALCL. Immunohistochemical stainings of lymph node biopsy revealed positivity of cJun, JunB as well as PDGFRα in the tumor cells. Due to very promising data on current studies with Cere-mediated conditional NPM-ALK knockdown mice (JunB and cJun dependent PDGFRα tyrosine kinase expression reveals imatinib/tilotinin treatment as effective therapeutic strategy for ALK driven lymphomas, Laimer et al., in submission) the possibility of inhibition of the PDGFR with imatinib was discussed with the patient and informed consent was obtained. Within 2 weeks of imatinib treatment B-symptoms declined, lymph node shrinkage was observed and complete remission was documented by PET-CT. Five weeks after start of therapy the patient is still in complete remission. This is the first documented case of a patient with ALK+ALCL responsive to the tyrosine kinase inhibitor imatinib. Despite of the short time of treatment so far, these data highlight a novel therapeutic strategy in refractory ALCL.

249 RESPONSE TO LENALIDOMIDE IN HEAVILY PRE-TREATED ANGIOIMMUNOBLASTIC T-CELL-LYMPHOMA (AITL)

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Background: Angioimmunoblastic T-cell lymphoma (AITL) is a rare peripheral T-cell lymphoma with generally aggressive course though spontaneous remissions are described. Treatment options considered are corticosteroids and chemotherapy. Relapses occur in 30%, but are usually responsive to autologous stem cell transplantation. Imatinib is a tyrosine kinase inhibitor with high affinity inhibition of the PDGF-receptor.

Methods: We report on lenalidomide treatment of two consecutive patients with recurrent AITL. Pts received lenalidomide therapy for a median of 6 cycles (range: 1-12 cycles).

Results: Case 1: 65 y.o. female, initially presenting with autoimmune haemolytic anemia, fever and fatigue. Diagnosis of AITL Stage IIIA in April 2008. Refractory disease to primary CHOP chemotherapy and Rituximab. Partial Response (PR) to 2nd – line IMVP-16 chemotherapy but persistent clinical symptoms of disease (fever,
chills, fatigue, frequent erythrocyte-transfusions). From Nov 2008 to Dec 2009 11 cycles of lenalidomide were applied. Initial dose 25 mg d1-21 q28. Dose reduction to 15 mg in cycle 4-7 and to 10 mg in cycle 8-11 due to grade 2 neutropenia. Efficacy: Complete Response according to RECIST after 5 cycles, clinical symptoms completely resolved after 1st cycle. Duration of response 519 days. Reoccurrence of symptomatic disseminated disease in Apr 2010. Since Mai 2010 re-exposure to lenalidomide. Initial dose 10 mg d1-21 q28. Dose reduction to currently 5 mg every two days due to grade 2 neutropenia. Efficacy: PR after 5 cycles (37% decrease in sum of longest diameters (SLD)), no clinical symptoms since 1st cycle. Duration of 2nd response until now 271 days. Case 2: 49 y.o. male, presenting with fever, joint pain and dermal alterations. Diagnosis of AITL Stage IIIBE in Jul 2005. 5 prior lines of chemotherapy including CHOP, ICE, DHAP, high dose BEAM plus HSCT, gemcitabine and vinorelbine. From Jan to May 2010 lenalidomide was given at a dose of 25 mg d1-21 q28 in chemorefractory, progressive situation. Result: PR after 2 cycles (38% decrease in SLD), Progressive Disease after 4 cycles. Duration of response 130 days. Conclusions: Single agent lenalidomide demonstrated antitumor efficacy in two consecutive cases of AITL and may lead to durable remissions even at very small doses. Further investigations of lenalidomide as mono and combination-therapy in this rare disease are warranted.