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# Peripheral T/Nk Cell Lymphoma Clinic and Therapy

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T-cell non-Hodgkin's lymphomas (NHL) are rare in Europe and the United States, where they constitute about 15 to 20% of aggressive lymphomas (1,2,3,4). The prognostic significance of the immunophenotype has been explored in several studies (2,5,6,7) and conflicting results have been reported concerning the outcome of PTCL compared to that of B-cell lymphomas (BCL). PTCL patients were found to have equivalent, (5,8) or poorer prognoses than patients with BCL (6,7). However, PTCL represent an heterogeneous group of lymphomas and a wide variety of different histological subtypes have been recognized (9,10,11,12,13,14). The most common subtype is an heterogeneous group of PTCL not other specified (NOS) (9), followed by anaplastic large cell lymphoma (ALCL) (17), angioimmunoblastic lymphoma (AIL) (16,17). Although it was suggested that PTCL had low-grade or high-grade histological features, the prognostic significance of such a distinction has not been established.

The International Prognostic Index (IPI) Project (18) did not evaluate the influence of immunophenotype overall survival (OS), primarily because of the limited amount of phenotypic data available and the difficulty of prospectively studying a cohort of PTCL patients large enough to ensure statistical significance. The prognostic value of immunophenotype, using the REAL classification, was evaluated with stratification of other prognostic factors (3, 20). Although, the T-cell phenotype was an independent and significant prognostic factor, it was not possible to demonstrate a statistically significant effect on OS among the different histological

subtypes.

To better define the clinical outcomes of the different subtypes of T-cell lymphoma, 288 patients with a confirmed T-cell immunophenotype included in the prospective LNH87 protocol were compared to 1595 BCL patients of comparable histological grades (21). PTCL were classified as angioimmunoblastic (AIL) (23%), NOS (49%) or anaplastic large cell (ALCL) (20%) lymphomas.

The median age of the PTCL patients enrolled in the study was 56 years and that of BCL patients was 57 years. Several clinical parameters were significantly more prevalent in PTCL patients: male gender, advanced stage with multiple-node involvement, B-symptoms, BM involvement, hepatosplenomegaly and skin lesions. BCL patients had more localized stage and bulky disease. Significantly more PTCL patients with AIL presented with anemia, hypereosinophilia and hypergammaglobulinemia.

The CR rates were 54% and 63% for T-and B-cell NHL, respectively ( $p = 0.005$ ). However, it should be pointed out that, T-ALCL patients had the best CR rate (72%) which was significantly different from that of the non-ALCL PTCL (49%) ( $p = 0.002$ ).

The overall 5-years survival rates differed between PTCL (41%) and BCL (52%) ( $p = 0.0004$ ). Survival was also analyzed according to the histological subtypes. First, ALCL had a 5 years OS of 64% which was better than that of any subgroup of T- or B-cell NHL. Second, PTCL-NOS T-cell lymphoma had significantly lower survival rates when compared to diffuse large cell (centroblastic and immu-

noblastic) BCL patients. Third, the remaining subgroup including ALL, with a 31% probability of survival, had a worse outcome than diffuse B lymphomas (46%). Because of the better survival advantage for T-ALCL, multivariate analysis was performed only on patients with non-ALCL PTCL and BCL. Analysis was done using the IPI (age, stage, LDH, PS) as one factor. Non-ALCL T-cell lymphoma remained a significant ( $p=0.0004$ ) adverse prognostic factor.

This study confirmed that PTCL had severe disease at the time of presentation as already described (2,3) and might explain the lower CR rate observed in non-ALCL T-cell lymphoma as compared to B-cell NHL. Not surprisingly, this poorer response was translated into shorter OS and EFS. These results are in agreement with our previous study (2), but were not found in other retrospective studies (5,6,8) (table 1). In fact in the study of Kwak et al. (5) based on 98 diffuse large cell NHL, there was a trend favoring the better outcome of T-cell lymphomas. Because of the size of this population, it was possible to separate and analyze each of the major subgroups defined by the Kiel classification and to compare them to B-cell NHL. Only ALCL T-cell lymphomas had significantly better CR rates and survival, and thus should be clearly separated from the other groups, for the analysis of the significance of immunophenotype as a prognostic factor. With risk stratification according to the IPI score, the OS was significantly worse for non-ALCL T lymphomas, but this difference was mainly found with an IPI score  $\geq 2$ , even when all PTCL were analyzed together. In multivariate analysis, non-ALCL T-cell character appeared to be an independent adverse prognostic factor and should be incorporated in the definition of prognostic groups. The poor prognosis of peripheral T-cell lymphoma has been reported in most series (2,3,6,8,19,20,21). With the intensive regimens used in the LNH87 study, a 41 % 5 year survival rate is observed however, the 23 % 5-year survival rate for patients with 3 or more adverse prognostic factors cries out for new strategies (22).

#### **Angioimmunoblastic T-cell Lymphoma**

Patients with angioimmunoblastic T-cell lymphoma typically present with generalized adenopathy, fever, weight loss, skin rash, polyclonal hypergammaglobulinemia, autoimmune manifestations that can include a positive Coombs test, and frequent infection. The most complicated factors in the care of patients in whom angioimmu-

noblastic-like T-cell lymphoma is considered is whether the patient has a "benign" condition mimicking T-cell lymphoma.

The complete remission rates varied from 60% to 100% with no obvious advantage to any particular treatment regimen. An important study reported by Siegert et al. tested the relative merits of initial prednisone therapy versus initial treatment with an aggressive combination-chemotherapy regimen (23). The conclusion of the study was that patients with angioimmunoblastic lymphadenopathy-type were doing better with an effective combination-chemotherapy regimen. Other treatments used for angioimmunoblastic T-cell lymphoma have included cyclosporin, low-dose oral methotrexate, interferon and autologous transplantation (22).

#### **Anaplastic large lymphoma**

Primary systemic anaplastic large cell lymphoma (ALCL) accounts for 2%-8% of all lymphomas. Two distinct clinical forms of primary ALCL are now recognized: limited to the skin and systemic (9). Clear clinicopathologic differences have been found between AKL-positive and ALK-negative subtypes in most studies (24, 25, 26). ALK-positive patients were much younger and ALCL occurred during the first three decades of life. B symptoms were observed in both groups and ALK-positive patients had significantly better performance status and fewer had above normal LDH levels. An increased incidence of extranodal involvement was seen in the AKL-negative group. Skin, bone and soft tissues were commonly affected extranodal sites. The ALK-positive group had lower IPI scores than the ALK-negative group. ALK expression is closely correlated with age and IPI. Patients with ALCL-T had significantly better survival than those with non-ALCL T-cell lymphoma (27, 20, 24). Shiota et al reported (24) a significant prognostic difference between ALK-positive and ALK-negative ALCL, with the former having a far better 5-year survival rate (80%) the later (33%). The European Intergroup Study of ALCL (28) compared the results and prognoses of 235 children enrolled in trials designed to treat childhood ALCL with short and intensive chemotherapy. Multivariate analysis has brought to light three prognostic factors : 1) mediastinal involvement , 2) visceral involvement, 3) skin lesions. For the good-prognosis group with 0 factors, the 3-years EFS was 87% for the poor-risk group with at least 2 factors, the expected 3-year EFS was 87%; for the poor-risk group with at least 2 factors, the expected 3-year OS was 61%.

**Table 1.** Comparison of response rate and survival between B cell lymphoma and peripheral T cell lymphoma patients

	NHL B/T Nb	CR		(n.s)	Survival		(%)	Freedom from progression		(%)
		B	T		B	T		B	T	
Coiffier (2)	253/108	71	72	(n.s)	60	55	(0.04)	80	40	(0.002)
Armitage (6)	91/19	74	53	(n.s)	50	41	(0.08)	75	70	(0.14)
Cheng (8)	36/34	67	62	(n.s)	NP	NP	(0.05)	NP	NP	NP
Kwak (5)	77/21	84	95	(0.19)	52	79	(0.08)	38	53	(0.14)
Lippman (7)	20/83	62	50	(0.31)	NP	NP	(0.23)	NP	NP	(0.01)
Gisselbrecht	1 595/288	63	54	(0.005)	53	41	(0.004)	42	33	(0.0001)

n.s : Non significant - NP : Not precised

ALCL accounts for only 10% to 15% of all childhood non-Hodgkin's lymphomas. In most European studies, ALCL is considered to be a separate entity and is treated with either a short and intensive chemotherapy regimen, as for B-cell lymphoma (29) or with more prolonged chemotherapy derived from T-cell lymphoma protocols (30). The opportunity to classify this disease into low and high risk cases according to IPI score and ALK-positivity is highly relevant for the design of optimal therapeutic strategies. No randomized studies comparing different regimens have been reported so far. For children, the BFM group, after a cytoreductive prephase, stratified treatment into 3 branches with different dose intensity : stage I and II resected, stage II nonresected and stage III, stage IV or multifocal bone disease, similar 5-years EFS rate were observed at 76% and 79% respectively (29). In adults most investigators reported that the ALCL response rate to chemotherapy was good. The age-adjusted IPI within the good-prognosis group of ALK-positive lymphomas showed that the 5-year OS rate was 94% for the 0-1 factors versus 41% for  $\geq 2$  factors have still a poor prognosis and new approaches are needed. Guidelines for the treatment of ALCL in the absence of large prospective study in adults are not easy. Two factors should be taken in consideration. ALK positivity and adverse prognostic factors.

#### **Extranodal Natural Killer/T-cell Lymphoma, nasal type**

Nasal NK/T-cell lymphoma more commonly affects men. The tumor typically presents with nasal symptoms. Cranial nerves may also be involved, but meningeal involvement is not common (31). Systemic dissemination is often late but clinically very aggressive. Favorite sites include skin, gut, and testis, sites where CD56 is normally expressed. Patients also present with a primary tumor in one of these sites.

Local radiotherapy and chemotherapy are both effective treatments for primary nasal lymphoma. However, with radiotherapy or chemotherapy alone, treatment failure is still common (31, 32, 33). For patients with disseminated disease at presentation or at disease progression, the disease is almost invariably fatal. The optimal timing of radiotherapy in relation to chemotherapy is also uncertain. The presence of residual tumor cells after 3 months of initial chemotherapy is usually indicative of inadequate response to therapy. A decision has to be made at that time to give local radiotherapy early and to switch to an alternative chemotherapy regime.

#### **Hepatosplenic T-cell Lymphoma**

Hepatosplenic lymphoma is an aggressive subtype of extra-nodal lymphoma accounting for less than 5% of all peripheral T-cell lymphomas(34).

The disease occurs mainly in young men, presenting with splenomegaly and very often hepatomegaly but without peripheral lymphadenopathy. More than one half of the patients have B symptoms. The association with a hemophagocytic syndrome has been occasionally mentioned.

Due to the rarity of the disease, information regarding therapeutic results has been obtained from single or sporadic reported cases with short follow-up at the time when they were published, resulting in a considerable heterogeneity of treatment modalities(35). Treatment options have included – in addition to splenectomy performed for diagnostic purposes – steroids, alkylating agents, anthracycline-containing CHOP-like regimens, purine analogs, and autologous and allogeneic hematopoietic stem cell transplantation. From available reports, it appears that there are very few, if any, long-survival patients. All of the patients have died and median survival time was 12 months.

### Enteropathy-type T-cell Lymphoma

Enteropathy-type intestinal T-cell lymphoma is a rare type of non-Hodgkin's lymphoma comprising less than 1% of all non-Hodgkin's lymphoma.

The most common presenting symptoms for enteropathy-type intestinal T-cell lymphoma were abdominal pain (84%), weight loss (81%), diarrhea (39%), and vomiting (29%) (36). Small bowel perforation or small bowel obstruction were presenting features in 42%. In the series, from Ireland, a similar proportion of patients without preceding celiac disease (60%) presented with intestinal obstruction of perforation (37). Night sweats and fevers are uncommon presenting symptoms in enteropathy-type intestinal T-cell lymphoma. Abdominal masses are uncommon (16%), and none of the patients in the UK series had peripheral lymphadenopathy at presentation (36).

It is now widely intestinal T-cell lymphoma should receive combination chemotherapy. The most commonly used regimen for patients with enteropathy-type intestinal T-cell lymphoma is CHOP. However, the use of combination chemotherapy in these patients is complicated, and less than 50% of patients in the Southampton series completed their planned courses of chemotherapy (36).

Response data are available from only one of the prior studies (36). Of 24 patients treated with combination chemotherapy, ten (41%) achieved a complete remission and four (16%) a partial response. The actuarial 1-year and 5 year overall-survival rates were 39% and 20% respectively.

### Subcutaneous panniculitis-like T-cell lymphoma

This entity represents the least well-defined and, perhaps, rarest of the subtypes of peripheral T-cell lymphoma.

The clinical behavior of typical patients includes presentation with subcutaneous, sometimes painful nodules that can resemble lipomas. The lesions are typically first seen on the extremities and follow a several-year course of waxing and waning, but ultimately progressing. The nodules can sometimes ulcerate. Although responses to standard combination-chemotherapy regimens are frequently seen (38, 39, 40), complete responses are not common, and the responses are rarely durable. Involved-field radiation has a high response rate, but the disease frequently relapses in unirradiated sites. The hemophagocytic syndrome is a well-described complication of subcutaneous panniculitis-like T-cell lymphoma (41). In cases reporting this

association, it has been an often fatal complication. However, in many cases, the disease remains confined to the subcutaneous tissue, although any organ can be involved.

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