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Update on T-cell lymphoma

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The classification of non-Hodgkin lymphoma (NHL) has evolved steadily over the past several decades. In the 1950s, Rappaport et al. [1] recognized the importance of the growth pattern in NHL and used the pattern, in addition to the cell size and shape, as the basis of a clinically relevant classification. In the 1970s, recognition that NHL cells were derived from T or B cells led to the immunologically based classification of Lukes and Collins [2] and the Kiel classification of Lennert and colleagues [3]. The Working Formulation was proposed in 1982 in an attempt to unify the various classification systems [4].

Over the past 30 years, there has been an increasing understanding of the genetic abnormalities and immunologic characteristics of NHL. This knowledge has led to further subclassification of NHL with the recognition of new subtypes within both the B-cell and T-cell categories. In 1994, a group of European and American pathologists proposed a new classification of lymphoid neoplasms based upon contemporary morphologic, immunologic and genetic techniques [5]. This eventually formed the basis for a new World Health Organization (WHO) classification of the hematopoietic and lymphoid neoplasms, utilizing many of the new diagnostic techniques in an attempt to recognize all of the existing and new entities [6]. This new classification was tested on a cohort of 1403 cases of NHL obtained worldwide in the International Non-Hodgkin Lymphoma Classification Project [7]. Of these cases, only 7% represented a subtype of peripheral T-cell lymphoma (PTCL) and 2.4% were anaplastic large T/null-cell lymphoma (ALCL). However, even in a study of this size, not enough cases were present to investigate the various subtypes of PTCL.

In Western countries, PTCL accounts for 15–20% of aggressive lymphomas and 5–10% of all NHLs [8, 9]. On the Asian continent, this number is higher with ∼15–20% of all lymphomas classified as PTCL or NK/T-cell lymphoma (NKTCL) [9, 10]. The majority of patients with PTCL present with advanced stage disease and one-third of patients have extranodal involvement at the time of diagnosis. Despite aggressive chemotherapy, the majority of patients with most subtypes of PTCL do not enjoy long-term disease-free survival.

A recent large international retrospective study [13, 14] evaluated the various subtypes of lymphoma and other disorders found among cases from 22 sites in North America, Europe and Asia. The subtypes documented upon review are found in Table 1. A diagnosis of PTCL or NKTCL was confirmed in 1153 of the cases (87.8%). The most common subtype identified was PTCL, not otherwise specified (NOS) (25.9%), with the second most common subtype being the angioimmunoblastic type (18.5%). NKTCL represented 10.4% and adult T-cell leukemia/lymphoma (ATLL) 9.6% of the cases. The next most common subtypes were anaplastic large cell lymphoma (ALCL) ALK+ (6.6%), ALCL ALK– (5.5%) and enteropathy-type PTCL (4.7%). All the other specific subtypes of PTCL represented <2% of the total. Some other T-cell disorders not specifically included in the study (1.8%) were also diagnosed, and 10.4% of the cases were misclassified and found to be other disorders including Hodgkin lymphoma (3%), B-cell lymphoma (1.4%) or a diagnosis other than lymphoma (2.3%). Only 3.6% of the cases could not be adequately classified, usually due to inadequate material or technical factors.

The diagnostic agreement from the experts with the consensus diagnosis was 97% for ALCL ALK+, 93% for ATLL, 92% for NKTCL, 81% for angioimmunoblastic type, 79% for enteropathy-type, 75% for PTCL-NOS and subcutaneous panniculitis-like type, 74% for ALCL ALK–, 72% for hepatosplenic type and only 66% for primary cutaneous ALCL. A change in diagnosis 1 with the addition of the clinical data occurred in 6.4% of the cases overall, and was highest (38.7%) for a change from PTCL-NOS to ATLL due to a need for specific serologic or molecular data documenting viral infection for the diagnosis of ATLL. The overall agreement upon re-review of a subset of the cases by the five regional experts was 81% (range, 67–95%).

The relative frequencies of the various lymphoma subtypes by geographic region were interesting. PTCL-NOS was the most common subtype in both North America and Europe, whereas NKTCL and ATLL were common in the Far East. ATLL was frequent in Japan, but was not found in the other countries in the Far East, whereas NKTCL made up 44% of the cases in the Far East excluding Japan. ALCL ALK+ was most common in North America, whereas enteropathy-type PTCL was most common in Europe (mainly Norway). Interestingly, angioimmunoblastic type was most common in Europe compared with the other regions. Primary cutaneous ALCL was higher in North America than in Europe, possibly due to referral of such cases to dermatologists and dermatopathologists in Europe, whereas systemic and cutaneous ALCL, enteropathy-type and hepatosplenic PTCL were uncommon in the Far East.

The clinical characteristics of the various subtypes of PTCL and NKTCL were interesting. All the subtypes were found more

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Table 1. Distribution of the 1314 cases by the consensus diagnosis

Diagnosis	Cases	%
Peripheral T-cell lymphoma (PTCL): NOS PTCL unspecified type (301), PTCL lymphoepithelioid type (28), PTCL parafollicular type (6), PTCL T-zone type (5)	340	25.9
Angioimmunoblastic	243	18.5
Natural killer/T-cell lymphoma (NKTCL): nasal NKTCL (92), extranasal NKTCL (35), unclassifiable NK-cell (7), aggressive NK-cell leukemia (2)	136	10.4
Adult T-cell leukemia/lymphoma (ATLL)	126	9.6
Anaplastic large cell lymphoma (ALCL): ALK+ ALCL, common type (79), ALCL small cell type (4), ALCL lymphohistiocytic type (4)	87	6.6
ALCL ALK–	72	5.5
Enteropathy-type	62	4.7
Primary cutaneous ALCL	22	1.7
Hepatosplenic	19	1.4
Subcutaneous panniculitis-like	12	0.9
Peripheral γ/δ T-cell	1	0.1
Unclassifiable PTCL	33	2.5
Other T-cell disorders: mycosis fungoides/Sézary syndrome (8), precursor T-cell lymphoblastic (12), T-cell prolymphocytic leukemia (2), T-cell large granular lymphocytic leukemia (2)	24	1.8
Other disorders (not T-cell): blastic 'NK-cell' lymphoma (2), T-cell/histiocyte-rich large B-cell NHL (3), diffuse large B-cell lymphoma (13), B-cell lymphoma, other (2), Hodgkin lymphoma (40), unclassifiable lymphoma (9), diagnosis other than lymphoma (30), case unclassifiable (38)	137	10.4

commonly in male patients. The median age for all patients was 62 years. However, several subtypes had a median age that was much younger, including ALCL ALK+ (33 years), hepatosplenic type (34 years) and subcutaneous panniculitis-like PTCL (33 years). Most of the subtypes also had a high percentage of patients with advanced stage III/IV disease, except primary cutaneous ALCL and nasal NKTCL. Bone marrow involvement was frequent in the hepatosplenic type, but was uncommon in nasal NKTCL, ALCL of all types, enteropathy-type and subcutaneous panniculitis-like PTCL.

Overall survival for many of the subtypes of PTCL and NKTCL is poor. The 5-year overall survival (OS) for PTCL-NOS, angioimmunoblastic and for all NK/T-cell lymphomas was 32% compared with only 14% for ATLL. Anaplastic large cell lymphoma ALK+ demonstrated the best 5-year OS (70%), with ALCL ALK– having an intermediate 5-year OS (49%). Although rare, primary cutaneous ALCL had an excellent 5-year OS of 90%. The 5-year OS for subcutaneous panniculitis-like PTCL was also good (64%) as compared with enteropathy-type (20%) and hepatosplenic PTCL (7%). The 5-year OS for nasal NKTCL was 42%, with an apparent plateau, compared with a 5-year OS of only 9% for extra-nasal NKTCL and aggressive and/or unclassifiable NK/T-cell leukemia/lymphoma. Five-year failure-free survival (FFS) was as follows: PTCL-NOS (20%), angioimmunoblastic (18%), ATLL (12%), nasal NKTCL (29%), extra-nasal NKTCL (6%), ALCL ALK+ (60%), ALCL ALK– (36%). For the less common subtypes, the 5-year FFS was as follows: primary cutaneous ALCL (55%), subcutaneous panniculitis-like PTCL (24%), enteropathy-type PTCL (4%) and hepatosplenic PTCL (0%).

Since this is a retrospective study of cases from 22 worldwide centers, the initial therapeutic approaches varied widely. The majority of patients (>85%) with the most common subtypes such as PTCL-NOS, angioimmunoblastic type, ATLL, ALCL ALK+ and ALK–, received an anthracycline-containing regimen. Radiation therapy was used mostly for patients with localized disease, such as primary cutaneous ALCL and for patients with nasal NKTCL. Unlike diffuse large B-cell lymphoma (DLBCL), the majority of patients with PTCL or NKTCL, other than ALCL ALK+, did not benefit from the use of an anthracycline-containing regimen over a non-anthracycline-containing regimen.

Most aggressive PTCLs and NKTCLs have traditionally been treated with an anthracycline-containing regimen and complete response rates of 50–70% have been reported [11–15]. However, patients in these studies have a long-term survival of only 10–30%. Our international study confirms the very poor prognosis of patients with the aggressive forms of PTCL and NKTCL. For the most common subtypes, PTCL-NOS and angioimmunoblastic lymphoma, patients treated with an anthracycline-containing regimen had the same long-term survival as those treated with non-anthracycline-containing regimens. Clearly, better therapeutic regimens are needed to improve the long-term outcome of these patients. Novel agents and combinations such as gemcitabine, histone deacetylase inhibitors and monoclonal antibodies are currently in clinical trials for various types of T-cell lymphoma [16–18].

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