Special Article

T-Cell Lymphomas in South America and Europe

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Peripheral T-cell lymphomas are a group of rare neoplasms originating from clonal proliferation of mature post-thymic lymphocytes with different entities having specific biological characteristics and clinical features. As natural killer cells are closely related to T-cells, natural killer-cell lymphomas are also part of the group. The current World Health Organization classification recognizes four categories of T/natural killer-cell lymphomas with respect to their presentation: disseminated (leukemic), nodal, extranodal and cutaneous. Geographic variations in the distribution of these diseases are well documented: nodal subtypes are more frequent in Europe and North America, while extranodal forms, including natural killer-cell lymphomas, occur almost exclusively in Asia and South America. On the whole, T-cell lymphomas are more common in Asia than in western countries, usually affect adults, with a higher tendency in men, and, excluding a few subtypes, usually have an aggressive course and poor prognosis. Apart from anaplastic lymphoma kinase-positive anaplastic large cell lymphoma, that have a good outcome, other nodal and extranodal forms have a 5-year overall survival of about 30%. According to the principal prognostic indexes, the majority of patients are allocated to the unfavorable subset. In the past, the rarity of these diseases prevented progress in the understanding of their biology and improvements in the efficaciousness of therapy. Recently, international projects devoted to these diseases created networks promoting investigations on T-cell lymphomas. These projects are the basis of forthcoming cooperative, large scale trials to detail biologic characteristics of each sub-entity and to possibly individuate targets for new therapies.

Keywords: *Lymphoma, T-cell/epidemiology; Killer-cells, natural; Prognosis; Lymphoma, T- cell/pathology; Lymphoma, T-Cell/classification; Hematologic neoplasms; South America; Europe*

Introduction

T-cell Lymphomas constitute a heterogeneous group of rare disorders that have different biological and clinical profiles resulting from clonal proliferation of mature post-thymic lymphocytes, in the majority of the cases from either the $CD8^+$ or $CD4^+$ lineages. Most, therefore, express αβ T cell receptors. Since natural killer (NK) cells are closely related to T-cells, neoplasms derived from these are also placed within this group. Until the 1970s they were not distinguished from lymphomas originating from the B-cell lineages but considered a major histologic subtype within a single group that included all lymphomas that was only poorly described according to growth pattern.[1] Only after the immune system was better characterized, lymphomas began to be subdivided into B and T cell lineages and started to be considered separate entities.[2-4] The role of the immunophenotype in distinguishing disease entities was affirmed by the Revised European-American Lymphoma (REAL) classification published in 1994[5] which was subsequently confirmed by the World Health Organization (WHO) project.[6]

The 2008 WHO classification for hematopoietic malignancies[7] roughly divides the mature forms of T-cell and NK-cell malignancies (otherwise reported as peripheral T-cell lymphomas - PTCLs) into four categories according to their presentation: predominantly leukemic (disseminated), nodal, extranodal and cutaneous. In each category, entities are further differentiated based on morphologic, genotypic, genetic and immunohistochemical criteria, as well as clinical behavior.[7]

Compared to B-cell lymphomas, mature T/NK-cell lymphomas are uncommon malignancies accounting for 10 to 15% of all non-Hodgkin lymphomas (NHL), with well documented geographic variations.[8-10] In the western hemisphere T-cell lymphomas represent 5 to 10% of all NHL[8,11-13] with an overall incidence rate of 0.5-2 per 100,000 inhabitants per year.[14] Surveillance Epidemiology and End Results (SEER) data (2004-2008)[15] report an age-adjusted incidence rate (IR) in the US for T/NK-cell

lymphomas of 1.8/100,000 men and women per year. In Europe, data from the Cancer Registry Based project on Haematologic malignancies (HAEMACARE)[16] on lymphoid malignancies diagnosed in 2000-2002 and archived in 44 European cancer registries present a crude IR of 1.13 per 100,000 inhabitants per year for mature T/NK-cell neoplasms. Out of the 66371 cases diagnosed with a lymphoproliferative disorder in the period 2000-2002, 2527 (3.8%) were mature forms of T/NK-cell lymphoma. These patients can be subdivided into two different categories, the first includes cutaneous forms (n = 1208, IR = 0.54 per 100,000 inhabitants per year) and the other grouping disseminated, nodal or extranodal PTCLs (n = 1319, IR = 0.59 per 100,000 inhabitants per year). These two categories have been investigated with respect to survival confirming very different outcomes for the two populations: period estimates for 2000-2002 of 5-year relative survival were calculated on a mean number of 1046.5 cases of cutaneous PTCLs and 987.5 cases of other T/NK-cell lymphomas leading to a 83.4% 5-year relative survival for cutaneous PTCLs and a 38.6% 5-year relative survival for non-cutaneous PTCLs.[17]

PTCLs are relatively more frequent in Asia[12,18,19] and in Central and South America,[20-22] where approximately 15% to 20% of lymphoma are diagnosed as PTCL or NK/T-cell lymphomas, with NK-cell lymphomas (NKCL) occurring almost exclusively in Asia and South America. The differences in the geographic distribution of T-cell lymphoma may result from a real higher incidence in eastern countries as well as the relatively lower frequency in Asia of many B-cell lymphomas such as follicular lymphoma.[23] Indeed, race has been reported to correlate with the incidence of B-cell lymphomas as they are more frequently detected in Whites than in Asians, while the incidences for T-cell lymphomas for Whites and Asians are comparable.[23] In addition to race-linked factors, a possible cause of geographic variations could be the higher prevalence of viral infections, particularly the human T-cell lymphotropic virus type 1 (HTLV-1) in eastern counties compared to Europe and the US, an infection that appears to be related to the onset of adult T-cell leukemia/lymphoma (ATLL) and NK-cell neoplasms.[23-26]

The mature forms of T/NK-cell lymphomas usually affect the adult population, with a median age between 55 to 60 years and a slight predominance in men.[13,14,27,28] Most of the patients present with an advanced stage disease[11,13,27-29] and constitutional symptoms[11,13,27] and a non-ambulatory performance status in one third of the cases.[27,29]

PTCLs with cutaneous presentation may have a relatively benign protracted course while nodal and extranodal T-cell lymphomas have an aggressive clinical behavior and poor prognosis. Indeed, with the exclusion of anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma and indolent mycosis fungoides which have good survival rates,[30] the prognosis of PTCLs is dismal with a 5-year survival near to 30% on the whole.

Geographic distribution: the international projects

The first attempt to systematically study the distribution of NHL subtypes across geographic regions based on collaborative international efforts was performed after the NHL Classification Project was carried out.[31] The project collected 1403 cases (diagnosed from 1988-1990) from nine institutions in eight different geographic regions thought to have a case base representative of their geographical location. Out of the cases collected, upon a review process involving five expert hematopathologists, 25 (1.8%) were found to have diagnoses other than NHL and were excluded from the analysis and 1378 were confirmed to be NHL. Analyses confirmed statistical evidence that the distribution among the major histologic subtypes of NHL differed substantially by geographical region. According to the consensus diagnosis, a greater percentage of follicular lymphoma was seen in North America, London and Cape Town (28%-32%) than at the other sites (8%-18%). PTCLs made up a higher percentage of the cases from London (8%), Cape Town (8%) and Hong Kong (10%) than from the other sites (1%-6%). Primary mediastinal large B-cell lymphomas and mantle cell lymphomas were more common in Locarno and Bellinzona (9% and 14%, respectively) than at the other sites (0%-4% and 1%-8%, respectively). Angiocentric nasal T/NK-cell tumors were only seen in Hong Kong (8%) and, to a lesser extent, in Lyon (2%).

The project included 129 cases (9.4% of 1378) of PTCLs, 33 of which were anaplastic large cell lymphomas (ALCLs: 2.4%).[12]

The frequencies of the 96 cases of non-anaplastic PTCLs reported in the project varied geographically ranging from 1.5% in Vancouver to 18.3% in Hong Kong.[8] According to the consensus diagnosis, most of the 96 non-anaplastic cases were reported as PTCL not otherwise specified (NOS) (53 patients, 55%), followed by angiocentric nasal type (19 patients, 20%), which were almost exclusively recorded in Hong Kong (16 cases), and angioimmunoblastic T-cell lymphoma (AITL) (17 cases, 18%), whereas the other subtypes were rare.

Later on, the International T-cell Lymphoma Project (ITLP) collected 1314 cases of T/NK-cell lymphomas from 22 Institutions worldwide[28] with diagnoses made from 1990-2002. The results confirm those reported by the NHL Classification Project with respect to the geographical distribution of subtypes: higher rates of leukemic and NK-cell neoplasms were recorded in Asia (25% and 22.4%, respectively) than in North America (2% and 5.1%, respectively) and in Europe (1% and 4.3%, respectively). On the other hand, PTCL-NOS were more frequent in both North America and Europe (34.4% and 34.3%, respectively) than in Asia (22.4%). ALK-positive ALCLs were most common in North America (16%) whereas the enteropathy

subtype was most common in Europe (9.1%). Notably, AITL were reported to be more common in Europe (28.7%) compared to North America (16%) and Asia (17.9%). With respect to rarer extranodal forms (excluding primary cutaneous ALCL), most of the cases were diagnosed in Europe (2.8%) and only a few cases were reported in North America and Asia (1.6% and 1.5%, respectively).

More recently the ITLP launched the T-Cell Project, a study aimed at investigating clinical and biological characteristics of aggressive nodal and extranodal PTCLs by means of prospective data collection. An overview of the study is described elsewhere.[32,33] The study started enrolling patients at the end of 2006 and so far 790 patients have been registered from 63 Institutions distributed in four different geographic regions: Europe (Italy: 38 sites; UK: 4; Switzerland: 3; Slovakia: 1; Spain: 1), United States (Memorial Sloan-Kettering Cancer Center, M. D. Anderson Cancer Center, University of Nebraska Medical University, Stamford University, Cleveland Clinic Foundation, Fred Hutchinson Cancer Research Center), South America (Argentina: 3 sites; Brazil: 2; Chile: 1; Uruguay: 1) and the Middle/Far East (South Korea: 1; Hong Kong: 1; Israel: 1) with total patients of 338, 136, 170 and 146, respectively. Four additional sites recently joined the project, but up to now no patients have been registered. The preliminary analysis of the first 524 patients included in the T-Cell Project and presented at the 11th International Conference on Malignant Lymphoma in Lugano[34] supports the previously described geographical variations for these disorders.

At present, 755 patients have been validated in the study. Out of these, 18 were considered after review as misdiagnosed by the local pathologist and were excluded. Out of the remaining 737 patients, PTCLs-NOS account for 285 cases (38.7%) and AITL for only 127 cases (17.2%); on the other hand, 94 (12.7%) cases of ALK-negative ALCL were registered. The AITL and ALK-negative ALCL cohorts are about half and twice, respectively of what was expected. The distribution of cases for the whole population according to histologic subtypes is summarized in Table 1.

Table 2 shows the distribution of histologic entities by geographic region according to reviewed diagnosis. PTCLs-NOS represent the most common subtype in Europe, North America and South America (40%, 42% and 42%, respectively), whereas NKCL is the most common subtype in Asia (31%). Both ALK-negative and ALK-positive ALCLs are prevalent in South America (23% and 8%, respectively).

Table 1 - Histologic subtype distribution according to reviewed histology of 737 cases registered in the T-Cell Project

	n	%
PTCL-NOS	283	38.4
AITL	123	16.7
ALCL, ALK$^-$	99	13.4
ALCL, ALK$^+$	49	6.6
NK/T nasal, nasal type, lymphoma/leukemia	92	12.5
Enteropathy-type T-cell lymphoma	35	4.7
Hepatosplenic T-cell lymphoma	13	1.8
Subcutaneous panniculitis-like T-cell lymphoma	10	1.4
Peripheral gamma-delta T-cell lymphoma	8	1.1
Unclassifiable, T-cell	20	2.7
Unclassifiable, NK-cell	7	0.7
Total	737	100.0

PTCL: Peripheral T-cell lymphomas; NOS: Not otherwise specified; AITL: Angioimmunoblastic T-cell lymphoma; ALCL: Anaplastic large cel lymphomas; ALK: Anaplastic lymphoma kinase; NK: Natural killerl

Table 2 - Histologic subtype distribution (%) according to reviewed histology of 737 cases registered in the T-cell project by geographic region

	Overall	Europe	USA	South America	Middle/ Far East
PTCL-NOS	38	40	42	42	26
AITL	17	20	21	8	15
ALCL, ALK$^-$	13	14	9	23	6
ALCL, ALK$^+$	7	6	8	8	4
NK/T nasal, nasal type, lymphoma/leukemia	13	6	9	13	31
Other histologies	12	14	11	6	18

PTCL: Peripheral T-cell lymphomas; NOS: Not otherwise specified; AITL: Angioimmunoblastic T-cell lymphoma; ALCL: Anaplastic large cell lymphomas; ALK: Anaplastic lymphoma kinase; NK: Natural killer

Europe

So far, the European cohort of the T-Cell Project includes 317 validated cases. The overall distributions of histologic subtypes in the European countries - Italy, UK and others counties (Switzerland, Slovakia and Spain, grouped together) – are presented in Table 3. About three quarters of the European patients have been diagnosed with PTCLs-NOS (40%), AITL (20%) or ALK-negative ALCLs (14%).

Table 3 shows that significant differences between countries are evident. ALK-negative ALCL is the most common subtype in the UK (20%) and rarely diagnosed in Switzerland, Slovakia and Spain. In Italy they represent 14% of the cases and are less frequent than their ALK-positive counterpart (8%); Italy has the highest rate for this subtype. Extranodal forms of PTCLs reported in Europe have singular distributions for all countries: the majority of NKCL and enteropathy-type PTCL (11% in both cases) and two out of three cases of gamma/delta peripheral PTCL were registered in Switzerland, Slovakia and Spain, while three out of the four European cases of subcutaneous panniculitis-like PTCL were diagnosed in Italy.

Clinical characteristics of patients registered by European sites are summarized in Table 4.

Table 3 - Histologic subtype distribution by country of the 317 cases registered for European sites in the T-cell project

	Overall		Italy		United Kingdom		Others *	
	n	%	n	%	n	%	n	%
PTCL-NOS	127	40	99	41	19	41	9	33
AITL	63	20	47	19	10	22	6	22
ALCL, ALK^-	44	14	34	14	9	20	1	4
ALCL, ALK^+	21	6	18	8	2	4	1	4
NK/T nasal, nasal type	19	6	13	5	3	7	3	11
Enteropathy-type	22	7	17	7	2	4	3	11
Hepatosplenic	5	2	5	2	-	-	-	-
Other histologies	16	5	11	4	1	2	4	15
Subcutaneous panniculitis-like	4		3		1		-	
Peripheral γδ T-cell lymphomas	3		1		-		2	
Unclassifiable T/NK PTCLs	9		7		-		2	
Total	317		244		46		27	

PTCL: Peripheral T-cell lymphomas; NOS: Not otherwise specified; AITL: Angioimmunoblastic T-cell lymphoma; ALCL: Anaplastic large cell lymphomas; ALK: Anaplastic lymphoma kinase; NK: Natural killer
* Switzerland, Slovakia and Spain

Table 4 - Clinical characteristics of 317 patients registered by European sites in the T-cell project

	Overall			Italy		United Kingdom		Others *	
	n = 317	57		n = 244	58	n = 46	57	n = 27	55
	Total cases	n	%	Total cases	%	Total cases	%	Total cases	%
Age (≥ 60 yrs)	317	152	48	244	50	46	41	27	37
Gender (Male)		196	62		59		70		70
ECOG (>1)	247	51	21	190	20	34	12	23	35
B-symptoms		131	53		52		44		74
Disease-related discomfort		184	74		74		71		87
Stage (III-IV)	225	180	80	174	83	31	64	20	75
Bone marrow (involvement)	201	51	25	155	27	28	14	18	28
IPI low-low/ intermediate	214	123	57	169	54	31	77	14	57
PIT low-low/intermediate	194	114	59	153	56	27	78	14	50

ECOG: Eastern Cooperative Oncology Group classification; IPI: International Prognostic Index; PIT: Prognostic index of peripheral T-cell lymphomas
* Switzerland, Slovakia and Spain

South America

At present, 152 patients from South American countries were registered in the T-Cell Project. The overall distribution and the distribution by country – Chile, Brazil and Argentina/Uruguay – of different histologic entities are shown in Table 5.

As expected, the rate of PTCLs-NOS is similar to that of Europe (42%) and the percentages of ALK-negative ALCL and of NKCL are higher than in Europe (23% and 13%, respectively). Considering the distribution by country, the PTCL-NOS rate ranges from 19% in Brazil to 51% in other countries. Relative high rates of both ALK-negative (23%) and ALK-positive (8%) ALCLs have been registered in this area compared to Europe. The highest rate of ALK-negative ALCL was recorded in Brazil with 39% of cases, while in Argentina/Uruguay the percentage (11%) is lower than the mean value of South America for this subtype. Similarly, the highest rate of ALK-positive ALCLs (12%) was reported in Brazil. The rate of NKCLs in South America is on the whole double of that in Europe at 15% in both Brazil and Argentina/Uruguay. Interestingly, no extranodal forms of PTCLs other than NKCL were reported for Brazil, while these forms are more common in Chile; the only case of enteropathy-type PTCL and five out of the six cases of subcutaneous panniculitis-like PTCL were diagnosed in this country.

Of note, AITL is confirmed as a rare subtype in this geographic region accounting for a maximum of 10% of cases registered in Brazil.

Clinical characteristics of patients registered by South American sites are summarized in Table 6.

Table 5 - Histologic subtype distribution by country of 152 cases registered by South American sites in the T-cell project

	Overall		Chile		Brazil		Others *	
	n	%	n	%	n	%	n	%
PTCL-NOS	64	42	43	51	8	19	13	49
AITL	12	8	6	7	4	10	2	8
ALCL, ALK$^-$	35	23	16	19	16	39	3	11
ALCL, ALK$^+$	12	8	4	5	5	12	3	11
NK/T nasal, nasal type	19	13	9	11	6	15	4	15
Enteropathy-type	6	4	5	6	-	-	1	3
Subcutaneous panniculitis-like	1	< 1	1	1	-	-	-	-
Unclassifiable T/NK PTCLs	3	2	-	-	2	5	1	3
Total	152		84		41		27	

PTCL: Peripheral T-cell lymphomas; NOS: Not otherwise specified; AITL: Angioimmunoblastic T-cell lymphoma; ALCL: Anaplastic large cell lymphomas; ALK: Anaplastic lymphoma kinase; NK: Natural killer
* Argentina and Uruguay

Table 6 - Clinical characteristics of 152 patients registered by South American sites in the T-cell project

	Overall			Chile		Brazil		Others *	
	n = 152	51		n = 84	52	n = 41	47	n = 27	51
	Total cases	n	%	Total cases	%	Total cases	%	Total cases	%
Age (≥ 60 yrs)	152	48	32	84	31	41	27	27	41
Gender (Male)		89	59		63		49		59
ECOG (> 1)	140	55	21	84	56	40	8	16	31
B-symptoms		75	54		54		52		56
Discomfort disease-related		108	77		77		70		94
Stage (III-IV)	110	59	54	81	53	16	50	13	62
Bone marrow (involvement)	93	11	12	65	8	16	12	12	33
IPI low-low/ intermediate	119	80	67	81	63	25	84	13	62
PIT low-low/intermediate	104	66	63	67	58	25	84	12	50

ECOG: Eastern Cooperative Oncology Group classification; IPI: International Prognostic Index; PIT: Prognostic index of peripheral T-cell lymphomas
* Argentina and Uruguay

In conclusion the preliminary data coming from the T-Cell Project confirm the characteristic and peculiar profiles for Europe and South America in the distribution of all subtypes of aggressive PTCLs except PTCL-NOS. AITL is confirmed as a distinctive disorder in Europe, while in South America, NKCL and ALK-negative ALCL represent the most common subtypes.

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