El T-Cell Project: lecciones de estudios prospectivos observacionales

The T-Cell Project: lessons from observational prospective studies

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Abstract

Peripheral T-cell and NK-cell lymphomas (PTCLs) are a group of diverse lymphoproliferative disorders including very different entities with diverse biological and clinical behavior. The updated version of the WHO classification provided significant advances in both nodal and extranodal mature T-cell and NK-cell lymphoma, which have led to the introduction of new provisional entities, mainly thanks to the results of the genomic studies that have been performed since the 4th edition was published in 2008. However, these new information have not translated so far in clinical practice and remain restricted to clinical trials. Prognosis of PTCLs has been extensively studied by means of retrospective evaluations. Since these kind of studies carry on biases, the International T-Cell Lymphoma Project, after its retrospective study on 1,314 patients, promoted in 2006 the T-Cell Project, an observational prospective registry aiming at improving information on prognosis of the two most frequent subtypes of PTCLs (peripheral T-cell lymphoma, not otherwise specified and angioimmunoblastic T-cell lymphoma) and to get better insight the clinical an biological characteristics of other rarer nodal and

extranodal PTCLs. The T-Cell project is a well consolidated network having at present 74 participating sites from four regional areas.
The prognosis for PTCLs remains poor, mainly due to low response rates to induction therapy, to the short duration of response with standard combination chemotherapy regimens and to the controversial role of transplant as consolidation after achievement of response with first line therapy. However, in the recent years a number of novel agents have been approved for the treatment of PTCLs in the relapsed/refractory setting, and some trials have been opened for this subset of patients. Moreover, in the last decade advances in the biological and genetic characteristics of these diseases have been made, and some other are planned or ongoing. The biobank of the T-Cell Project and the wide cooperation in it of a number of institutions could serve for future studies on developing trials specific for the different subtypes for the first line treatment exploring novel combinations in front line approaches.

Introduction

Peripheral T-cell and NK-cell lymphomas (PTCLs) comprise an extremely heterogeneous group of rare, aggressive disorders that are derived from post-thymic lymphoid cells at different stages of differentiation with different morphological patterns, phenotypes, and clinical presentation[1,2]. The diversity of PTCLs reflects the diverse cells from which they can originate[3-12].

PTCLs account for 5-10% of all cases of non-Hodgkin lymphomas (NHL) in the Western hemisphere, with an overall incidence of 0.5-2 per 100,000 per year[10,13]. By some estimates, the incidence of PTCLs has increased significantly in recent years in some industrialized countries, the growth being driven by an ageing population[14] or because of an apparent growth in incidence because of improvements in diagnosis techniques[15].

The WHO 2008 classification[1] roughly divides PTCLs into leukemic (disseminated), cutaneous, other extranodal, and nodal sub-types, which are distinct with respect to pathology, clinical presentation, response to therapy, and expression of surface markers. Each of these groups is further sub-classified into a variety of different entities based on clinico-biological features. PTCLs have a striking epidemiological distribution, with higher incidence in Asia, where their percentage is as high as 24%, and in Central and South America, where they represent 15%-20% of NHL[10,16-24].

The differences in the geographic distribution of PTCLs 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, that are more common in the US and in Europe[14]. An additional reason could be the higher prevalence of viral infections, particularly the human T-cell lymphotropic virus type 1 (HTLV-1) in eastern countries 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[14,22,25,26].

What we know about the prognosis of T Cell Lymphomas

Due to the rarity of the disease and the lack of randomized clinical trials, there is currently no consensus with respect to front-line therapy in PTCLs. As reported by the International T-cell Lymphoma Project (ITCLP)[27] and the T-Cell Project[28], patients are commonly given anthracyclines (CHOP/CHOP-like), in a minority of cases with etoposide (CHOEP/CHOEP-like), which produce unsatisfactorily results with respect to aggressive B-cell lymphomas[29]. Results of some phase II trials show that early consolidation with autologous stem cell transplant (ASCT) could improve the patient's outcome, particularly those achieving complete response (CR) after induction chemotherapy. However, approximately 30% of patients is going to progress after induction, preventing them to possibly benefit from a consolidative ASCT[30-32]. The overall survival (OS) of PTCLs is generally poor, with 5-yr OS significantly lower than that of aggressive B-cell NHLs (41% vs. 53%; p=0.0004)[29]. The survival rates ranges from 15% to 50% 5-year OS, excluding anaplastic lymphoma kinase (ALK)-positive ana-

plastic large cell lymphoma (ALCL), which have a 5-yr OS around 70%[27,28]. The generally poor outcome of PTCLs asks for the urgent need of more effective treatment approaches. Recently, a series of novel agents have been approved for the relapsed/refractory setting, and hopefully in the next years an improvement in the outcome could be reached[33].
Several studies have been performed to assess the contribution of a number of clinical and biological factors to the prognosis of PTCLs[34-40]. In most of them, adverse prognostic features such as poor performance status, advanced stage, presence of extranodal sites, bulky disease, and high LDH levels were significantly correlated with shorter OS. Even if the usefulness of the International Prognostic Index (IPI), defined for aggressive B-cell lymphomas, has provided some insight into the distinct prognostic subtypes of PTCLs, it was not developed with data from cases of T-cell malignancies, and thus is considered largely suboptimal.
Although some prognostic models have been developed based exclusively on PTCLs cases, these models do not embrace the biological and clinical heterogeneity of the diseases. Unluckily, these models have established an unfortunate fact, there is no such thing as favourable risk PTCL.
In order to better define the clinical outcome of T-cell lymphomas grouped within the broad category of PTCL-NOS as a single entity, and to assess a prognostic model specifically devised for patients with this uncommon disease, the Intergruppo Italiano Linfomi (now Fondazione Italiana Linfomi, FIL) performed a large study on 385 patients diagnosed and treated in the 1990s and defined a prognostic model, called PIT, based on age (>60 yr), Performance Status (ECOG PS 2 or higher), LDH level above upper normal range, and bone-marrow involvement[38].
One major limitation of the existing studies seeking to define the natural history of PTCLs is the fact that they are all retrospective in nature. These available data-sets are based on analyses performed on data collected over long periods of time, relying on often tedious and inefficient chart reviews. Moreover, many lines of clinical or laboratory data now considered critical in emerging prognostic models were not collected in these older series of patients. Additionally, it is well recognized that these types of retrospective analyses are limited by the fact that there is no guarantee that collected data are based on real consecutive cases, and are thus highly subject to selection bias.
Recently, the role of biological features of the disease is emerging as an important issue not only for understanding its pathogenesis but also for prognosis and for addressing specific biologic targets altered in the neoplasia. An updated version of the PIT (modified-PIT or m-PIT) was proposed replacing bone marrow involvement with Ki67 rate of expression, resulting in a more robust tool than the PIT[41]. The expression of Th1- or Th2-associated antigens or activated T-cell receptor has been evaluated in a series of T-NHLs. The pattern of expression of such antigens was correlated with the specific subtype of nodal T-cell lymphoma (AILT, ALCL, and PTCL-NOS) and allowed the identification of subgroups of PTCL-NOS patients with different probabilities of survival. In particular, patients with PTCL-NOS expressing one of Th1 or Th2 antigens tended to show favorable prognosis as compared with cases not expressing Th1 or Th2 antigens[42].
Moreover, in the last years, Gene Expression Profiling (GEP) studies have been conducted to better classify and risk stratify PTCLs. A recent work in GEP reveals that angioimmunoblastic T-cell lymphoma (AITL) is closely associated with follicular helper cells, and that AITL gene signature included genes involved in humoral immune response, recruitment of inflammatory cells, and modulation of vasculogenesis and the extracellular matrix[43]. The use of microarrays to analyse GEP allowed to distinguish between AITL, ALCL and T-lymphoblastic lymphoma[44]; with the same technique these authors managed to identify 3 molecular subgroups amongst the PTCL-NOS with different gene expression that translated in different outcome[44]. This is a very preliminary work, however, and confirmatory studies are needed.
The updated version of the WHO classification[2] provided significant advances in both nodal and extranodal mature T-cell and NK-cell lymphoma, which have led to the introduction of new provisional entities, mainly thanks to the results of the genomic studies that have been performed since the 4th edition was published in 2008. These new findings can help clinicians in more accurately predicting the prognosis of the diverse entities. Unfortunately, these informations haven't translated at present into

a guide to choose the most indicated therapeutic approach for each single subtype.

What is next: The T-Cell Project

The International T-Cell Lymphoma Project (ITCLP), that represents the largest clinicopathologic study of PTCL and NKTCL (Natural killer/T-cell lymphoma) organized to date[27], retrospectively collected a cohort of 1,314 cases of PTCL and NKTCL from 22 centres world-wide, consisting of patients with previously untreated PTCL or NKTCL who were diagnosed between 1990 and 2002. This retrospective review proposed five major objectives: (a) to evaluate the ability of hematopathologists to apply the WHO classification to a large group of cases; (b) to evaluate the role of clinical data in the diagnosis of the lymphoma subtypes; (c) to determine the relative frequencies and geographic variation of the subtypes; (d) to determine clinical correlations, including clinical features, treatment, and survival outcomes; and (e) to evaluate the percentage of transformed cells, Ki67 proliferation, Epstein-Barr virus (EBV) status, and phenotypic markers. Tissue biopsies, immunophenotypic markers, molecular genetic studies, and clinical information from consecutive patients at each site were reviewed by panels of four expert hematopathologists and classified according to the WHO classification. A diagnosis of PTCL or NKTCL was confirmed in 1,153 (87.8%) of the cases. These data revealed that the most common subtypes were PTCL not otherwise specified (NOS; 25.9%), angioimmunoblastic type (18.5%), NKTCL (10.4%), and adult T-cell leukaemia/lymphoma (ATLL; 9.6%). Alarmingly, misclassification occurred in 10.4% of the cases, and a marked variation in the frequency of the various subtypes as a function of its geographic region was also found. The ITCLP confirmed that the clinical outcome for patients with most of these lymphoma subtypes was poor with few to no standards of care[27]. Based on its retrospective experience and on the success of the F2-study (that prospectively collected 1,093 patients with follicular lymphoma in 2 years)[45-47], in 2006 the ITCLP promoted the T-Cell Project (NCT01142674). The study builds on the retrospective study carried on by the network, and it was designed as a prospective collection of information potentially useful to predict the prognosis of newly diagnosed patients with the more frequent subtypes of peripheral T-cell lymphoma (*peripheral T-cell lymphoma unspecified* [PTCL-NOS], and *angioimmunoblastic T-cell lymphoma* [AITL]) and to better define clinical characteristics and outcome of the more uncommon subtypes (*extranodal NK/T-cell lymphoma* [NKTCL]*; enteropathy-type T-cell lymphoma* [EATL]*; hepatosplenic T-cell lymphoma* [HSTCL]*; peripheral γδ T-cell Lymphoma* [PγδT-CL]*; subcutaneous panniculitis-like T-cell lymphoma* [SPLTCL]*; anaplastic large-cell lymphoma, T/null cell, primary systemic type* [ALCL]).

The T-Cell Project is conducted in compliance with the Helsinki Declaration of 1975 as revised in 1983, was approved by the appropriate research ethic committees, and required each patient to provide written informed consent before registration. Between September 2006 and June 2016, 1,481 cases of PTCLs have been registered by 74 Institutions located in Europe, USA, South America, and Middle and Far East.

Registration of patients in the study and data collection were performed on-line by means of electronic Case Report Forms on a dedicated website complying with all the rules to assure protection in web communication and patient privacy and confidentiality (www.tcellproject.org). Data access and management was regulated by the use of passwords with different level of admittance, providing that subject confidentiality was respected.

Preliminary results have been already published and presented at various international congresses[19,48-51]. The most recent results achieved from the analysis of the first 1308 patients registered by 73 sites from 14 countries world-wide until January 2015 have been presented during the 13 ICML in Lugano, in June 2015[28]. Among 1308 patients (pts), 1248 were validated (22 pts were excluded for various reasons and 38 considered as misdiagnosed after review). PTCL-NOS is the most frequent subtype, accounting for 451 cases (36%). Distribution of subtypes among different geographic areas superimposes literature data, AITL being more frequent in Europe and USA (21% each) ALCL, ALK- in South America (25%) and NK-cell in Asia (29%). Most patients were at low/low-intermediate risk according to both IPI and PIT (61% and 60%). Therapy data were available for 959 pts. Chemotherapy alone or in combination with radiotherapy was the preferred choice in 90% of pts. Anthracycline- and etoposide-

containing regimens were adopted in 84% and 22% of pts, respectively (both in 12%). Stem cell transplant was adopted to consolidate initial response in 7% of pts, with different geographic distribution (USA 14%, EU 8%, Asia 6%, South America 2%). With induction therapy 451 (54%) pts achieved a CR and 159 (18%) a partial response (PR). After a median follow-up of 35 months, 518 deaths have been recorded (41%). Five-year OS and progression-free survival (PFS) were 44%, (95% CI 40-47) and 33% (95% CI 30-37), respectively. The ALCL,ALK+ showed the best 5-yr OS (73%, 95% CI 61-82).

Thus, the data coming from the T-Cell Project superimpose those of the retrospective effort[27] both in terms of proportion of subtypes, regional distribution, treatment, and outcome. Also the results of the central review process, performed so far in 573 patients registered in the T-Cell Project and recently published[52] lead to the same considerations and results.

Importantly, and unique to the T-Cell Project, it has already collected tissue from about 500 patients, representing 17 subtypes of PTCLs. This collection of tissue has been subject to expert histopathologic review, and is already providing key insights into those factors that most often lead to misdiagnosis[52]. Importantly, about 400 of these tissue specimens could be available for a number of genomic studies. The T-Cell Project aims at registration of 2,000 patients, accrual that is foreseen to be completed by the end of 2017.

Next Steps

Studies conducted so far are unfortunately insufficient to draw robust conclusions regarding important questions in the management of these diverse subtypes. For example, we do not have sufficient data to answer fundamental questions like: (a) have the newly approved drugs for PTCLs changed the natural history of relapsed or refractory disease in those countries that have approved these agents?; (b) how do patients with the more rare subtypes of PTCLs (like enteropathy associated T-cell lymphoma [EATL]; gamma-delta-TCL; or nasal NK-T cell lymphoma for example) do with autologous or allogeneic stem cell transplant?; (c) is the state of remission a critical determinant of long term benefit for patients with various subtypes of PTCL undergoing stem cell transplant?; (d) can we develop more refined prognostic models of individual PTCL subtypes that will be more informative than the present Prognostic Index derived from patients with PTCL-NOS (PIT)?; (e) what is the role of specific drugs (anthracyclines, platinums, etc.) on the overall response rate or complete remission rate for patients treated in the upfront setting?; (f) what is the role of high-dose therapy (HDT) and ASCT in the management of patients with these rare diseases?

Given the many questions we have answered over the past decade, and the enormous effort that has gone into configuring the infrastructure, we believe it would be of extreme importance to keep together the T-Cell Project network, capitalizing on the world-wide momentum, and giving birth to cooperation in clinical trials, possibly even in the first-line setting focusing to finally resolve the main remaining questions related to the behaviour of these truly orphan diseases.

Databases with the availability of some thousands of cases complete in their clinical data and an the creation of an international tissue catalogue including FFPE samples as well as frozen tissue have to be promoted, and to put accessible to research groups with a solid reputation in studying PTCLs at the molecular and translation level. The accrual of frozen material along with matching DNA will be strongly encouraged aiming to carry NGS (WES and WGS) studies. Fact is that the genomic landscape of PTCLs remains mainly unexplored, although recurrent genomic defects have been recently described in specific subtypes[43,44,53-61].

Possible objectives for the future are to: (a) define the presence and frequency of recurrent defects within an initial panel of 40 genes, known to be mutated in PTCLs. This panel will be expanded up to 200 with the acquisition of novel findings and/or focusing on additional genes within and/or regulating specific pathways (i.e. Jak/STAT, PI3K/AKT, etc.); (b) discover novel viral/pathogen(s) in EBV negative NK-T-cell lymphoma and to stratify the EBV positive cases, by linking the EBV gene expression and viral stains to specific tumoural populations.

Further goals that can be achieved with the creation of an international tissue bank are as follows: (a) development of innovative molecular tools for the better classification, differential diagnosis and prognosis of these neoplasms [that can be based on small sets of genes or miRNAs defined by discriminant

component analysis and translated to platforms like Nanostring, applicable to the routine diagnostics]; (b) development of *in vitro*, *ex vivo* and *in vivo* models to tests novel therapeutic targets; (c) construction of tissue micro arrays for protein validation or FISH studies put forward by molecular studies.

Conclusions

T-cell lymphomas are rare neoplasms that represent a diagnostic challenge with limited information on best practices and the most effective therapies. Given the rarity of these malignancies, registry studies, like the T-Cell Project, could provide invaluable information that aid the clinician and the researcher alike to further advance the field and answer critical questions that allow improved patient care and outcomes. Without international collaboration and instrumental effort into enrolling patients onto these registries and following their progress, making progress will remain challenging. To our knowledge, the T-Cell Project is the largest ongoing prospective registry at present, and this exceptional position could help in providing answers to critical questions integral to improving the care of patients with PTCLs. This unique registry of patients collected from all over the world, coupled with a precious biorepository, offers the opportunity to build future treatment platforms predicated on our biological understanding of the disease, which we anticipate will lead to the development of subtype specific treatments for patients and medical professions confronted by this heterogeneous and challenging disease.

Declaración de conflictos de interés:
Los autores declaran que no poseen conflictos de interés.

References

1. Swerdlow S, Campo E, Harris N, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th edition. Lyon, IARC Press, 2008.
2. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms. 2016. DOI: 10.1182/blood-2016-01-643569
3. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol 1999; 17(12):3835–3849
4. Jaffe ES, Harris NL Tumours of haematopoietic and lymphoid tissues—pathology and genetics, World Health Organization of Tumours. Lyon, IARC Press, 2001.
5. Picker LJ, Weiss LM, Medeiros LJ, et al. Immunophenotypic criteria for the diagnosis of non-Hodgkin's lymphoma. Am J Pathol 1987; 128(1):181–201.
6. Cooke CB, Krenacs L, Stetler-Stevenson M, et al. Hepatosplenic T-cell lymphoma: a distinct clinicopathologic entity of cytotoxic gamma delta T-cell origin. Blood 1996; 88(11):4265–4274.
7. Delves PJ, Roitt IM The immune system. First of two parts. N Engl J Med 2000; 343(1):37–49.
8. Delves PJ, Roitt IM The immune system. Second of two parts. N Engl J Med 2000; 343(2):108–117.
9. O'Leary HM, Savage KJ Novel therapies in peripheral T-cell lymphomas. Curr Oncol Rep 2008; 10(5):404–411.
10. Savage KJ Peripheral T-cell Lymphomas. Blood Rev 2007; 21(4):201–216.
11. Campo E, Swerdlow SH, Harris NL, et al. The 2008 WHO classification of lymphoid neoplasms and beyond : evolving concepts and practical applications The 2008 WHO classification of lymphoid neoplasms and beyond : evolving concepts and practical applications. Blood 2011; 117(19):5019–5032.
12. Jones D, O'Hara C, Kraus MD, et al. Expression pattern of T-cell-associated chemokine receptors and their chemokines correlates with specific subtypes of T-cell non-Hodgkin lymphoma. Blood 2000; 96(2):685–690.
13. Luminari S, Federico M Other peripheral T-cell lymphomas; in The Lymphoid Neoplasms. Third Edition., Magrath IT (ed). London, Edward Arnold Ltd, 2010, pp.1400–1420.

14. Morton LM, Wang SS, Devesa SS, et al. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood 2006; 107(1):265–276.

15. Abouyabis AN, Shenoy PJ, Lechowicz MJ, et al. Incidence and outcomes of the peripheral T-cell lymphoma subtypes in the United States. Leuk Lymphoma 2008; 49(11):2099–2107.

16. Anderson JR, Armitage JO, Weisenburger DD Epidemiology of the non-Hodgkin's lymphomas: distributions of the major subtypes differ by geographic locations. Non-Hodgkin's Lymphoma Classification Project. Ann Oncol 1998; 9(7):717–720.

17. Nakamura S, Koshikawa T, Koike K, et al. Phenotypic analysis of peripheral T cell lymphoma among the Japanese. Acta Pathol Jpn 1993; 43(7-8):396–412.

18. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004; 104(5):1258–1265.

19. Bellei M, Chiattone CS, Luminari S, et al. T-cell lymphomas in South America and Europe. Rev Bras Hematol Hemoter 2012; 34(1):42–47.

20. Tse E, Kwong YL Treatment algorithms for mature T-cell and natural killer-cell neoplasms. Futur Oncol 2011; 7(9):1101–1112.

21. Gualco G, Domeny-Duarte P, Chioato L, et al. Clinicopathologic and molecular features of 122 Brazilian cases of nodal and extranodal NK/T-cell lymphoma, nasal type, with EBV subtyping analysis. Am J Surg Pathol 2011; 35(8):1195–1203.

22. Pombo de Oliveira MS, Matutes E, Schulz T, et al. T-cell malignancies in Brazil. Clinico-pathological and molecular studies of HTLV-I-positive and -negative cases. Int J Cancer 1995; 60(6):823–827.

23. Pombo De Oliveira MS, Loureiro P, Bittencourt A, et al. Geographic diversity of adult t-cell leukemia/lymphoma in Brazil. The Brazilian ATLL Study Group. Int J Cancer 1999; 83(3):291–298.

24. Cabrera ME, Martinez V, Nathwani BN, et al. Non-Hodgkin lymphoma in Chile: a review of 207 consecutive adult cases by a panel of five expert hematopathologists. Leuk & Lymphoma. 2012; 53:1311-1317.

25. Su IJ, Wang CH, Cheng AL, et al. Characterization of the spectrum of postthymic T-cell malignancies in Taiwan. A clinicopathologic study of HTLV-1-positive and HTLV-1-negative cases. Cancer 1988; 61(10):2060–2070.

26. Pombo-de-Oliveira MS, Carvalho SM, Borducchi D, et al. Adult T-cell leukemia/lymphoma and cluster of HTLV-I associated diseases in Brazilian settings. Leuk Lymphoma 2001; 42(1-2):135–144.

27. Vose JM, Armitage J et al. International peripheral T-cell and natural killer/T-cell lymphoma study: Pathology findings and clinical outcomes. International T-cell lymphoma project. J Clin Oncol 2008; 26(25):4124–4130.

28. Federico M, Bellei M, Pesce EA, et al. T-Cell Project: an international, prospective, observational study of patients with aggressive Peripheral NK/T-Cell Lymphoma: Lesson from the first 1308 patients. Hematol Oncol 2015; 33(Suppl1):100–180 Abstract 070.

29. Gisselbrecht C, Gaulard P, Lepage E, et al. Prognostic significance of T-cell phenotype in aggressive non-Hodgkin's lymphomas. Groupe d'Etudes des Lymphomes de l'Adulte (GELA). Blood 1998; 92(1):76–82.

30. Corradini P, Tarella C, Zallio F, et al. Long-term follow-up of patients with peripheral T-cell lymphomas treated up-front with high-dose chemotherapy followed by autologous stem cell transplantation. Leukemia 2006; 20(9):1533–8.

31. Rodriguez J, Conde E, Gutierrez A, et al. Frontline autologous stem cell transplantation in high-risk peripheral T-cell lymphoma: A prospective study from the Gel-Tamo Study Group. Eur J Haematol 2007; 79(1):32–38.

32. Mercadal S, Briones J, Xicoy B, et al. Intensive chemotherapy (high-dose CHOP/ESHAP regimen) followed by autologous stem-cell

transplantation in previously untreated patients with peripheral T-cell lymphoma. Ann Oncol 2008; 19(5):958–963.

33. Coiffier B, Federico M, Caballero D, et al. Therapeutic options in relapsed or refractory peripheral T-cell lymphoma. Cancer Treat Rev 2014; 40(9):1080–1088.
34. Rudiger T, Weisenburger DD, Anderson JR, et al. Peripheral T-cell lymphoma (excluding anaplastic large-cell lymphoma): results from the Non-Hodgkin's Lymphoma Classification Project. Ann Oncol 2002; 13(1):140–149.
35. Ascani S, Zinzani PL, Gherlinzoni F, et al. Peripheral T-cell lymphomas. Clinico-pathologic study of 168 cases diagnosed according to the R.E.A.L. Classification. Ann Oncol 1997; 8(6):583–592.
36. López-Guillermo A, Cid J, Salar A, et al. Peripheral T-cell lymphomas: Initial features, natural history, and prognostic factors in a series of 174 patients diagnosed according to the R.E.A.L. Classification. Ann Oncol 1998; 9(8):849–855.
37. Savage KJ, Chhanabhai M, Gascoyne RD, et al. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Ann Oncol 2004; 15(10):1467–1475.
38. Gallamini A, Stelitano C, Calvi R, et al. Peripheral T-cell lymphoma unspecified (PT-CL-U): A new prognostic model from a retrospective multicentric clinical study. Blood 2004; 103(7):2474–2479.
39. Zaja F, Russo D, Silvestri F, et al. Retrospective analysis of 23 cases with peripheral T-cell lymphoma, unspecified: clinical characteristics and outcome. Haematologica 1997; 82(2):171–177.
40. Ansell SM, Habermann TM, Kurtin PJ, et al. Predictive capacity of the International Prognostic Factor Index in patients with peripheral T-cell lymphoma. J Clin Oncol 1997; 15(6):2296–301.
41. Went P, Agostinelli C, Gallamini A, et al. Marker Expression in Peripheral T-Cell Lymphoma: A Proposed Clinical-Pathologic Prognostic Score. J Clin Oncol 2006; 24(16):2472–2479.
42. Tsuchiya T, Ohshima K, Karube K, et al. Th1, Th2, and activated T-cell marker and clinical prognosis in peripheral T-cell lymphoma, unspecified: comparison with AILD, ALCL, lymphoblastic lymphoma, and ATLL. Blood 2004; 103(1):236–41.
43. De Leval L, Rickman DS, Thielen C, et al. The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (TFH) cells. Blood 2007; 109(11):4952–4963.
44. Ballester B, Ramuz O, Gisselbrecht C, et al. Gene expression profiling identifies molecular subgroups among nodal peripheral T-cell lymphomas. Oncogene 2006; 25(10):1560–1570.
45. Federico M, Bellei M, Pro B, et al. The prognosis of follicular lymphomas: the F2-project. Haematol Rep 2006; 2(7):44–47.
46. Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J Clin Oncol 2009; 27(27):4555–62.
47. Solal-Céligny P, Bellei M, Marcheselli L, et al. Watchful waiting in low-tumor burden follicular lymphoma in the rituximab era: results of an F2-study database. J Clin Oncol 2012; 30(31):3848–53.
48. Federico M, Bellei M, Pesce E, et al. T-Cell Project: an international, longitudinal, observational study of patients with aggressive peripheral T-cell lymphoma. Rev Bras Hematol Hemoter 2009; 31(2):21–25.
49. Federico M, Bellei M, Pesce EA, et al. T-Cell Project: an International, Prospective, Observational Study of Patients with Aggressive Peripheral T-cell lymphoma. Analysys of first 524 patients. Ann Oncol 2011; 22(Suppl 4):Abs 241.
50. Horwitz SM, Bellei M, Marcheselli L, et al. The role of transplant in the treatment of Peripheral T-cell Lymphomas (PTCLs): an analysis from

the T-cell Project database. Hematol Oncol 2015; 33(Suppl 1):181–243 Abstract 247.

51. Bellei M, Marcheselli L, Pesce EA, et al. Clinical Characteristics and Patterns of Care of Patients (pts) with Peripheral T-cell Lymphoma (PTCLs) according to age at time of diagnosis: A T-Cell Project snapshot. Hematol Oncol 2015; 33(Suppl 1):181–231 Abstract 231.
52. Bellei M, Sabattini E, Pesce EA, et al. Pitfalls and major issues in the histologic diagnosis of peripheral T-cell lymphomas: results of the central review of 573 cases from the T-Cell Project, an international, cooperative study. Hematol Oncol 2016; DOI: 10.1002/hon.2316.
53. Zettl A, Rudiger T, Konrad MA, et al. Genomic profiling of peripheral T-cell lymphoma, unspecified, and anaplastic large T-cell lymphoma delineates novel recurrent chromosomal alterations. Am J Pathol 2004; 164(5):1837–1848.
54. Thorns C, Bastian B, Pinkel D, et al. Chromosomal aberrations in angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma unspecified: A matrix-based CGH approach. Genes Chromosom Cancer 2007; 46(1):37–44.
55. Nagel S, Leich E, Quentmeier H, et al. Amplification at 7q22 targets cyclin-dependent kinase 6 in T-cell lymphoma. Leukemia 2008; 22(2):387–392.
56. Salaverria I, Bea S, Lopez-Guillermo A, et al. Genomic profiling reveals different genetic aberrations in systemic ALK-positive and ALK-negative anaplastic large cell lymphomas. Br J Haematol 2008; 140(5):516–526.
57. Piccaluga PP, Agostinelli C, Califano A, et al. Gene expression analysis of angioimmunoblastic lymphoma indicates derivation from T follicular helper cells and vascular endothelial growth factor deregulation. Cancer Res 2007; 67(22):10703–10710.
58. Iqbal J, Weisenburger DD, Greiner TC, et al. Molecular signatures to improve diagnosis in peripheral T-cell lymphoma and prognostication in angioimmunoblastic T-cell lymphoma. Blood 2010; 115(5):1026–1036.
59. Martinez-Delgado B, Melendez B, Cuadros M, et al. Expression profiling of T-cell lymphomas differentiates peripheral and lymphoblastic lymphomas and defines survival related genes. Clin Cancer Res 2004; 10(15):4971–4982.
60. Cuadros M, Dave SS, Jaffe ES, et al. Identification of a proliferation signature related to survival in nodal peripheral T-cell lymphomas. J Clin Oncol 2007; 25(22):3321–3329.
61. Piccaluga PP, Agostinelli C, Califano A, et al. Gene expression analysis of peripheral T cell lymphoma, unspecified, reveals distinct profiles and new potential therapeutic targets. J Clin Invest 2007; 117(3):823–834.