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T Cell lymphomas: where we are and where we a re moving forward

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SUMMARY

Mature T-Cell Lymphomas (PTCLs) represent a heterogeneous group of haematological malignancies, with a fairly poor outcome. Due to their rarity, PTCLs are very poorly understood and information useful to develop more rational therapeutic approaches and substantially improve the prognosis are limited.

The T-Cell Project (TCP), launched a prospective collection of accurate data coming from patients with newly diagnosed PTCLs, with the aim of improving knowledge on these rare diseases. From Sept 2006 to Jan 2016, 1,439 cases have been registered by 74 Institutions world-wide. PTCL-NOS emerged as the most frequent subtype (36%). Combination chemotherapy was the preferred approach (90%), anthracycline-containing regimens being the favourite (84%). Consolidative ASCT was reported in 7%, with different geographic distribution. After induction therapy 54% achieved a CR and 18% a PR. After a median follow-up of 35 months, 5-yr OS and PFS were 44% and 33%, respectively. The ALCL, ALK+ showed the best 5-yr OS (73%).

The TCP is the largest ongoing prospective registry; and is now moving forward to the establishment of a large biorepository. This exceptional position could allow 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.

INTRODUCTION

PTCLs comprise a heterogeneous group of neoplasms that are derived from post-thymic lymphoid cells at different stages of differentiation with different morphological patterns, phenotypes, and clinical presentation (1, 2). PTCLs account for 5-10% of all lymphoproliferative disorders in the Western hemisphere (3, 4), with an overall incidence of 0.5-2 per 100,000 per year, and have a striking epidemiological distribution, with higher incidence in Asia (5).

PTCLs are highly diverse, reflecting the diverse cells from which they can originate (1, 6-10)

The 2008 World Health Organization classification includes 22 different subgroups, further sub-classified into leuke-

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mic, cutaneous, other extranodal, and nodal sub-types, which are distinct with respect to pathology, clinical presentation, response to therapy, and expression of surface markers. Moreover, PTCLs can be further divided into real and not real clinical entities based on clinico-biological features (1).

The real entities, which include Mycosis Fungoides (MF), Anaplastic Large Cell Lymphoma (ALCL) and Adult T-cell Leukaemia/Lymphoma (ATLL), along with the NK-derived lymphomas, can be easily diagnosed on the basis of morphologic, immunophentypic, and molecular features. All other entities which include nodal PTCLs [i.e., PTCL Not Otherwise Specified (PTCL-NOS) and Angioimmunoblastic T-cell Lymphoma (AITL)] together with all the other extra nodal PTCLs (i.e., Enteropathy Type T-cell Lymphoma, Hepatosplenic T-cell Lymphoma, Peripheral γδ T-cell Lymphoma and Subcutaneous Panniculitis T-cell Lymphoma) represent a diagnostic challenge and are generally included within the broad category of PTCLs.

The clinical features of PTCLs are extremely heterogeneous as they express more clinical diversity than B-cell non-Hodgkin's lymphomas (NHLs), and there is a close, though not absolute, relationship between some unusual clinical features and certain histological subtypes. Regardless of the subtype, the prognosis of patients with PTCLs is generally poor. Partially, this is due to the historical lack of therapies that are effective in treating T-cell lymphomas, thus forcing most patients with these neoplasms to be treated with regimens designed for diffuse large B-cell lymphoma (DLBCL) (11).

Because of their rarity and of heterogeneity among subtypes, PTCLs are very poorly understood, and few randomized trial comparing different approaches for these entities have been carried out. These facts have led to the unfortunate recognition that there is a small consensus on the optimal standard care of patients with this disease in the relapsed or upfront setting. Usually, front-line therapy for PTCLs relies on CHOP/CHOP-like regimens, with unsatisfactory results (12, 13).

Data published over the past decade by the International T-Cell Lymphoma Project on over 1.314 cases of PTCLs confirmed that most nodal and extranodal subtypes have a very low survival rates, with 5-year overall survival (OS) ranging from 14% to 49%, excluding anaplastic lymphoma kinase (ALK)-positive ALCL (5 yr OS 70%) (14). Overall, 5 yr OS of PTCLs is significantly lower than that of aggressive B-cell NHLs (41% vs 53%; p=0.0004) (15).

Results of some phase II trials show that early consolidation with autologous stem cell transplant (ASCT) could improve the patients 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 (16-18).

TREATMENT AND PROGNOSIS

The generally poor outcome of PTCLs asks for the urgent need of more effective treatment approaches. Recently, many single-arm phase I and phase II trials investigated on novel agents, particularly in the subset of refractory/relapsed disease, which have a par-

ticularly poor outcome. These include immunoconjugates, immunotherapies, and immunomodulators; histone deacetylase (HDAC) inhibitors; antifolates; fusion proteins; and nucleus analogues (19) (*Table 1*).

Several studies have been performed to assess the contribution of a number of clinical and biological factors to the prognosis of PTCLs (4, 20-25)we have evaluated the 96 cases of PTCL diagnosed within the Non-Hodgkin's Lymphoma Classification Project (NHLCP. 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. While the usefulness of the International Prognostic Index (IPI), defined initially 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 (23)we retrospectively analyzed 385 cases fulfilling the criteria defined by the World Health Organization classification. Factors associated with a worse overall survival (OS. Subsequently, the International Lymphoma Project 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. The study represented the largest clinicopathologic study of PTCL and NKTCL organized to date (14) in general, are associated with a poor clinical outcome.

Patients and methods

A cohort of 1,314 cases of PTCL and NKTCL was organized from 22 centers worldwide, consisting of patients with previously untreated PTCL or NKTCL who were diagnosed between 1990 and 2002. 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.

Results

A diagnosis of PTCL or NKTCL was confirmed in 1,153 (87.8%. 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;

TABLE 1 • Clinical trial efficacy results of novel single-agent treatment modalities.

Drug/regimen	Study	No. of evaluable patients	Type of patients	ORR (%)	Median PFS (months)
Alemtuzumab	Enblad, 2004	14	PTCL	36	NR
	Zinzani, 2005	10	PTCL-NOS and MF	60	NR
Alisertib	Friedberg, 2014	48	NHL (including PTCL)	27	NR
Belinostat	O'Connor, 2013	120	PTCL	26	NR
Bendamustine	Damaj, 2013	60	PTCL and CTCL	50	3.6
Bortezomib	Zinzani, 2007	12	PTCL and CTCL	67	NR
Brentuximab vedotin	Pro, 2012	58	ALCL	86	13.3
	Horwitz, 2014	34	PTCL	41	2.6
Denileukin diftitox	Dang, 2007	27	PTCL	48	6
Gemcitabine	Zinzani (1998)	13	PTCL-NOS and MF	69	NR
	Sallah, 2001	10	PTCL-NOS and CTCL	60	NR
	Zinzani, 2010	39	PTCL-NOS and MF	51	NR
Lenalidomide	Dueck, 2010	23	PTCL	30	3.2
	Zinzani, 2011	10	PTCL-NOS	30	NR
Mogamulizumab	Ishida, 2012	26	ATLL	50	5.2
	Ogura, 2014	37	CCR4$^+$ PTCL/CTCL	35	3.0
Pentostatin	Monfardini, 1996	37	NHL (including PTCL)	13	NR
	Tsimberidou, 2004	44	T-cell leukemias/ lymphomas	55	2.1
	Dang, 2003	14	T-cell NHL	50	6
Plitidepsin	Ribrag, 2013	29	PTCL	21	1.6
Pralatrexate	[a]O'Connor, 2009	29	T-cell lymphoma	54	NR
	O'Connor, 2011	109	PTCL	29	3.5
Romidepsin	Piekarz, 2011	45	PTCL and CTCL	38	NR
	Coiffier, 2012 (34) 2014	130	PTCL	25	4
Tipifarnib	Witzig, 2011	93	NHL (including PTCL)	20 (50 in PTCL)	NR
Zanolimumab	D'Amore, 2010	21	PTCL	24	NR

[a]All studies were phase II, except for this phase I/II study. Modified from Coiffier et al.(19).

c) to determine the relative frequencies and geographic variation of the subtypes;
d) to determine clinical correlations, including clinical features, treatment, and survival outcomes; e) to evaluate the percentage of transformed cells, Ki-67 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 International T-Cell Lymphoma Project confirmed that the clinical outcome for patients with most of these lymphoma subtypes was poor with few to no standards of care (14)in general, are associated with a poor clinical outcome.

Patients and methods

A cohort of 1,314 cases of PTCL and NKTCL was organized from 22 centers worldwide, consisting of patients with previously untreated PTCL or NKTCL who were diagnosed between 1990 and 2002. 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.

Results

A diagnosis of PTCL or NKTCL was confirmed in 1,153 (87.8%).

THE T-CELL LYMPHOMA PROJECT: A MAJOR ADVANCE IN PTCLS UNDERSTANDING

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.

Based on the experience of the International T-Cell Lymphoma Project, the success of the F2-study (that prospectively collected 1093 patients with follicular lymphoma in 2 years) (26-28), and the interest in the project expressed by participants to both these previous studies, in 2005 the T-Cell Project was promoted by the International T-Cell Lymphoma Project. 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* and *Angioimmunoblastic T-cell lymphoma*) and to better define clinical characteristics and outcome of the more uncommon subtypes (*Extranodal NK/T-cell lymphoma; Enteropathy-type T-cell lymphoma; Hepatosplenic T-cell lymphoma; Peripheral γδ T-cell Lymphoma; Subcutaneous panniculitis-like T-cell lymphoma; Anaplastic large-cell lymphoma, T/null cell, primary systemic type*).

The T-Cell Project (NCT01142674) was incepted in 2006. The study was conducted in compliance with the Helsinki Declaration of 1975 as revised in 1983, was approved by the appropriate research ethics committees, and required each patient to provide written informed consent before registration. Between September 2006 and January 2016, 1,439 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. Electronic Case Report Forms (ECRFs) were available at the Internet address: www.tcellproject.org. Patients registered into the study would not be identified by name on any study document to be collected, but were identified by a Subject Identification Number (Patient ID). The adoption of SSL03 technology assured protection in web communications of subject's clinical data. 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 (29-35). Moreover, the preliminary results of the first 1,000 cases have been discussed during an investigator meeting held in Modena on March 20-21, 2014.

The most recent results achieved from the analysis of the first 1308 patient registered by 73 sites from 14 countries world-wide until January 2015 have been presented during the 13 ICML in Lugano, in June 2015 (33). Among 1308 patients, 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 both to 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). These data were extremely well received, and considered to be essential in our efforts to better understand the natural history of these challenging and heterogeneous diseases, as well as the emerging patterns of care these patients receive around the world. In this respect, the bio-repository of the study could serve as a valuable source for the development of new and possibly more effective targeted therapies. The world-wide participation in the project demonstrates that the T-Cell Project has been exceedingly successful attracting some of the most prominent key opinion leaders from around the world to contribute to this effort. In addition, 15 new Institutions from five countries, representing expanding sites in Europe (Germany, Spain), South America (Ecuador, Peru and Venezuela) and Asia (Qatar, Siberia), have expressed an interest in participating in future efforts.

In addition, 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. Importantly, about 400 of these tissue specimens could be available for a number genomic studies.

FUTURE GOALS OF THE T-CELL LYMPHOMA RESEARCH: CAPITALIZING ON THE MOMENTUM

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 continue this effort, capitalizing on the world-wide momentum, 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 (36-46) not otherwise specified (PTCL NOS).

Possible objective 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.

Moreover, a web based platform should be implemented in order to provide a state-of-the-art web platform for collaborative clinical data collection and analysis compliant in NIH, HIPAA, 21 CFR Part 11 requirements and other regulatory guidelines, and will guarantee a careful management of security and confidentiality of data. These web platform should allow to collect on separate ECRFs details on patients features at diagnosis, at relapses/progressions and all treatment administered. With the new platform it should be also possible to manage the main project and all related sub-projects, collecting data from biological and genetic analyses. Including in the system a web Monitoring Tool could enable users to identify specific trends on charts and intensity geo-maps, make custom searches on clinical data, aggregate data coming from different data sources.

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 this malignancies, registry studies, like the TCP, 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.

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Conflict of interest

The authors declare that they have no competing interests.

REFERENCES

1. Swerdllow SH, Campo E HN. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon. IARC Press. 2008.
2. Elaine S. Jaffe, Nancy Lee Harris JWV. Tumours of Haematopoietic and Lymphoid Tissues - Pathology and Genetics, World Health Organization of Tumours. Lyon IARC Press. 2001.
3. Melnyk A, Rodriguez A, Pugh WC, Cabannillas F. Evaluation of the Revised European-American Lymphoma classification confirms the clinical relevance of immunophenotype in 560 cases of aggressive non-Hodgkin's lymphoma. Blood. 1997; 89: 4514-20.
4. Rüdiger T, Weisenburger DD, et al. Peripheral T-cell lymphoma (excluding anaplastic large-cell lymphoma): Results from the non-Hodgkin's lymphoma classification project. Ann Oncol. 2002; 13: 140-9.
5. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: Clinical features of the major histologic subtypes. J Clin Oncol. 1998; 16: 2780-95.
6. Picker LJ, Weiss LM, Medeiros LJ, et al. Immunophenotypic criteria for the diagnosis of non-Hodgkin's lymphoma. Am J Pathol. 1987; 128: 181-201.
7. Cooke CB, Krenacs L, et al. Hepatosplenic T-cell lymphoma: a distinct clinicopathologic entity of cytotoxic gamma delta T-cell origin. Blood. 1996; 88: 4265-74.
8. Delves PJ, Roitt IM. The immune system. First of two parts. N Engl J Med. 2000; 343: 37-49.
9. Delves P, Roitt I. Advances in immunology: The immune system - Second of two parts. N Engl J Med. 2000; 343: 108-17.
10. 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: 685-90.
11. Foss F. Hematology: relapsed and refractory PTCL-into the therapeutic abyss. Nat Rev Clin Oncol. 2011; 8: 321-2.
12. Schmitz N, Trümper L, Ziepert M, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood. 2010; 116: 3418-25.
13. Abouyabis AN, Shenoy PJ, Sinha R, et al. A Systematic Review and Meta-Analysis

of Front-line Anthracycline-Based Chemotherapy Regimens for Peripheral T-Cell Lymphoma. ISRN Hematol. 2011; 2011: 623924.
14. 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: 4124-30.
15. 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: 76-82.
16. 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: 1533-8.
17. Rodriguez, J, Conde E, 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: 32-8.
18. 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: 958-63.
19. Coiffier B, Federico M, Caballero D, et al. Therapeutic options in relapsed or refractory peripheral T-cell lymphoma. Cancer Treat Rev. 2014; 40: 1080-8.
20. 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: 583-92.
21. 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: 849-55.
22. Savage KJ, Chhanabhai M, Gascoyne RD, Connors JM. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Ann Oncol. 2004; 15: 1467-75.
23. Gallamini A, Stelitano C, Calvi R, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): A new prognostic model from a retrospective multicentric clinical study. Blood. 2004; 103: 2474-9.
24. Zaja F, Russo D, Silvestri F, et al. Retrospective analysis of 23 cases with peripheral T-cell lymphoma, unspecified: clinical characteristics and outcome. Haematologica. 82: 171-7.
25. 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: 2296-301.
26. Federico M, Bellei M, Pro A, et al. The prognosis of follicular lymphomas: the F2-project. Hameatologica Reports. 2006; 2: 44-7.
27. 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: 4555-62.
28. 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: 3848-53.
29. 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 (Suppl. 2): 21-5.
30. Federico M, Bellei M, et al. T-cell project: an international, prospective, observational study of patients with aggressive peripheral T-cell lymphoma. Ann Oncol. 2011; 22: Abstract 241.
31. Bellei M, Chiattone CS, Luminari S, et al. T-cell lymphomas in South america and europe. Rev Bras Hematol Hemoter. 2012; 34: 42-7.
32. Federico M, Bellei MLS. CD30 expression in Peripheral T-cell lymphomas (PTCLs): a subset analysis from the international, prospective T-cell Project. J Clin Oncol. 2015; 33: Abstract 8552.
33. Federico M, Bellei M, 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: 100-80 Abstract 070.
34. 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; 33:181-243. Abstract 247.
35. Bellei M, Marcheselli L, Pesce E, 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: 181-231. Abstract 231.
36. 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: 1837-48.
37. 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: 37-44.
38. Nagel S, Leich E, Quentmeier H, et al. Amplification at 7q22 targets cyclin-dependent kinase 6 in T-cell lymphoma. Leukemia. 2008; 22: 387-92.
39. Salaverria I, Bea S, et al. Genomic profiling reveals different genetic aberrations in systemic ALK-positive and ALK-negative anaplastic large cell lymphomas. Br J Haematol. 2008; 140: 516-26.
40. 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: 10703-10.
41. 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: 4952-63.
42. 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: 1026-36.
43. 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: 4971-82.
44. Ballester B, Ramuz O, Gisselbrecht C, et al. Gene expression profiling identifies molecular subgroups among nodal peripheral T-cell lymphomas. Oncogene. 2006; 25: 1560-70.
45. 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: 3321-9.
46. 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: 823-34.