Check for updates

Received: 9 January 2023 | Accepted: 7 June 2023

DOI: 10.1111/bjh.18941

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

ORIGINAL PAPER

Peripheral T-cell lymphoma with a T follicular-helper phenotype: A different entity? Results of the Spanish Real-T study

Alejandro Martín García-Sancho[1] | **Socorro M. Rodríguez-Pinilla**[2] | **Eva Domingo-Domenech**[3] | **Fina Climent**[4] | **Joaquín Sánchez-Garcia**[5] | **Javier López Jiménez**[6] | **Mónica García-Cosío Piqueras**[7] | **Josep Castellvi**[8] | **Ana Julia González**[9] | **Sonia González de Villambrosia**[10] | **José Gómez Codina**[11] | **Belén Navarro**[12] | **Guillermo Rodríguez**[13] | **Juan José Borrero**[14] | **Máximo Fraga**[15] | **Andrea Naves**[16] | **Lourdes Baeza**[16] | **Raúl Córdoba**[17]

[1]Department of Hematology, University Hospital of Salamanca (HUS/IBSAL), CIBERONC, University of Salamanca and Cancer Research Institute of Salamanca-IBMCC (USAL-CSIC), Salamanca, Spain

[2]Pathology Department, Hospital Universitario Fundación Jiménez Díaz, CIBERONC, Madrid, Spain

[3]Hematology Department, Institut Català d'Oncologia, L'Hospitalet de Llobregat, Spain

[4]Pathology Department, Hospital Universitari de Bellvitge-IDIBELL, L'Hospitalet de Llobregat, Spain

[5]Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Universidad de Córdoba, Hematology Department, Hospital Universitario Reina Sofía, Córdoba, Spain

[6]Hematology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain

[7]Anatomical Pathology Department, Hospital Universitario Ramón y Cajal, CIBERONC, Madrid, Spain

[8]Department of Pathology, Hospital Universitari Vall d'Hebron, Barcelona, Spain

[9]Hematology Department, Hospital Universitario Central de Asturias, Oviedo, Spain

[10]Hematology Department, Hospital Universitario Marqués de Valdecilla, Santander, Spain

[11]Medical Oncology Department, Hospital Universitari i Politècnic La Fe, Valencia, Spain

[12]Hematology Department, Hospital Universitario Puerta de Hierro, Madrid, Spain

[13]Hematology Department, Hospital Universitario Virgen del Rocío, Sevilla, Spain

[14]Anatomical Pathology Department, Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBIS)/Universidad de Sevilla, Sevilla, Spain

[15]Pathology Department, Hospital Clínico Universitario Santiago, Santiago de Compostela, Spain

[16]Medical Department, Takeda Farmacéutica España S.A., Madrid, Spain

[17]Hematology Department, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain

Correspondence
Alejandro Martín García-Sancho, Hematology Department, Hospital Universitario de Salamanca, IBSAL, CIBERONC, Centro de Investigación del Cáncer-IBMCC (USAL-CSIC), Salamanca, Spain.
Email: amartingar@usal.es

Funding information
Takeda Farmacéutica España, S.A.

Summary

Nodal peripheral T-cell lymphoma (PTCL) with a T follicular helper phenotype (PTCL-TFH) is a new type of PTCL. We aimed to define its clinical characteristics and prognosis compared to PTCL not otherwise specified (PTCL-NOS) and angioimmunoblastic T-cell lymphoma (AITL). This retrospective observational study included 175 patients diagnosed with PTCL between 2008 and 2013 in 13 Spanish sites. Patient diagnosis was centrally reviewed, and patients were reclassified according to the World Health Organization (WHO) 2016 criteria: 21 patients as PTCL-NOS, 55 as AITL and 23 as PTCL-TFH. Median follow-up was 56.07 months (95% CI 38.7–73.4). Progression-free survival (PFS) and overall survival (OS) were significantly

[Corrections made on 05 August 2023, after first online publication: The fifth author's affiliation was corrected in this version.]

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2023 The Authors. *British Journal of Haematology* published by British Society for Haematology and John Wiley & Sons Ltd.

higher in patients with PTCL-TFH than in those with PTCL-NOS and AITL (PFS, 24.6 months vs. 4.6 and 7.8 months, respectively, $p = 0.002$; OS, 52.6 months vs. 10.0 and 19.3 months, respectively, $p < 0.001$). Histological diagnosis maintained an independent influence on both PFS (hazard ratio [HR] 4.1 vs. PTCL-NOS, $p = 0.008$; HR 2.6 vs. AITL, $p = 0.047$) and OS (HR 5.7 vs. PTCL-NOS, $p = 0.004$; HR 2.6 vs. AITL, $p = 0.096$), regardless of the International Prognostic Index. These results suggest that PTCL-TFH could have more favourable features and prognosis than the other PTCL subtypes, although larger series are needed to corroborate these findings.

KEYWORDS

nodal peripheral T-cell lymphoma with a T-follicular helper phenotype, peripheral T-cell lymphoma, T-follicular helper cells

INTRODUCTION

Peripheral T-cell lymphomas (PTCL) represent a heterogeneous group of rare lymphoid neoplasms, historically difficult to diagnose and mostly with unfavourable prognosis.[1] Based on their clinical presentation, PTCL may be characterized as cutaneous, extranodal, nodal or leukaemic forms.[2,3] The most common disorders are angioimmunoblastic T cell lymphoma (AITL, 15%–30%), anaplastic large cell lymphoma (ALCL, ~15%), extranodal natural killer (NK) cell/T cell lymphoma (ENKTCL, ~10%) and intestinal T cell lymphomas (~5%–6%). However, up to 30% of cases not fulfilling criteria for other entities remain unclassifiable and are referred as PTCL "not otherwise specified" (PTCL-NOS).[2] PTCL subtypes differ in morphology, immunohistochemical phenotype, gene expression profile, clinical outcome and response to therapies.[2] Due to this complexity, the diagnosis and classification of PTCLs is challenging even for experienced hematopathologists, who may need to refer cases for a centralized review to reach an accurate diagnosis.

The World Health Organization (WHO) classification of malignant lymphomas update in 2016 included a new subgroup called "nodal lymphomas of T follicular helper (TFH) cell origin", an umbrella category created to highlight the spectrum of nodal lymphomas with a TFH phenotype, including three entities: (i) AITL, (ii) follicular T-cell lymphoma (FTCL) and (iii) nodal PTCL with a TFH phenotype (PTCL-TFH), all of which shared TFH-related antigens and recurrent genetic.[4] These tumours are believed to derive from a distinctive subset of T helper cells that play different roles in the germinal centre[5] and have a characteristic phenotype and genotype.[6,7] The TFH phenotype designation implies that the neoplastic cells express at least two, but ideally three, TFH-related antigens, including CD279/PD1, CD10, BCL6, CXCL13, ICOS, SAP and CCR5.

Prior to the WHO 2016 update, extensive panels of TFH markers—in the absence of morphological characteristics of AITL—were not routinely used to accurately diagnose all cases of PTCL. However, several nodal PTCL previously classified within the PTCL-NOS category have recently been shown to have a TFH-cell phenotype.[4] Such cases are now classified as PTCL-TFH, but, due to the low frequency and its recent definition, its clinical course and prognosis are not well delineated.[8,9] Although PCTL-TFH partially overlap with AITL[10] because they share morphological, phenotypic and genetic traits (similar gene expression profile signatures and common mutations in *TET2*, *DNMT3A* and *RHOA* genes),[11–16] they also have distinctive features.[2] Transition over time from one diagnosis to another in serial biopsies is another common feature between these two subtypes of T-cell lymphoma.[17] Some authors have suggested that PTCL-TFH may constitute a tumour-cell-rich variant of AITL,[18] but further evidence about the biological and clinical characteristics of PTCL-TFH is needed.

The aim of the present retrospective, observational study was to define the clinical characteristics and prognosis of this new PTCL-TFH entity compared to PTCL-NOS and AITL subtypes.

METHODS

Study design

Real-T was an observational, retrospective, multicentre study, in which a panel of experts conducted a central review of the initial diagnosis of a large series of patients with PTCL through phenotypic analysis of archived tumour samples.[19] Enrolment started in September 2015, and cases were collected from September 2015 to January 2016. A total of 175 patients diagnosed with PTCL between 2008 and 2013 in 13 Spanish centres were included in the study. Data analysis was carried out between February and April 2016. The study (TAK-HEM-2015-01) was classified as an Observational Study by the Spanish Agency of Medicines and Health Products (AEMPS) in February 2015 and was approved in April 2015 by an accredited Clinical Research Ethics Committee in Spain, according to the applicable Spanish legislation (Order SAS/3470/2009). The study was conducted in accordance with the International Conference on Harmonization Guidelines on Good Clinical Practice and the Declaration of Helsinki.[20,21] For this study, the Ethics Committee approved a patient information sheet and informed consent. This informed consent was obtained in writing from each patient

13652141, 2023, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bjh.18941 by Cstc Organización Central Om (Oficialia Mayor) (Utrc), Wiley Online Library on [26/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(alive patients) prior to their participation in the study. The Ethics Committee approves the exemption from obtaining consent, when obtaining such consent is not possible or represents an unreasonable effort (deceased patients), and when encoded data are processed, in accordance with Spanish legislation Order SAS/3470/2009 and Royal Decree 1716/20114. The study protocol was approved by the ethics committee of each one of the participating sites.

The main objective of the Real-T study was to assess the distribution of PTCL subtypes by reanalysis and reclassification of the tumour samples by a committee of experts, consisting of three independent hematopathologists, according to the WHO 2016 classification of lymphoid neoplasms. Data presented here is a subanalysis of the Real-T study that aims to define the clinical characteristics and prognosis of the new PTCL-TFH entity compared to PTCL-NOS and AITL.

Study population

Patients were eligible for enrolment in the Real-T study if they were diagnosed with nodal or extranodal PTCL in the 6-year period between 1 January 2008 and 31 December 2013, with available paraffin-embedded biopsy specimens from the initial diagnosis. Histologically confirmed PTCL subtypes allowed in the study, according to the WHO 2008 classification of lymphoid neoplasms,[22] were: extranodal NK-cell/T-cell lymphoma, nasal type; enteropathy-associated T-cell lymphoma; hepatosplenic T-cell lymphoma; PTCL-NOS; AITL; anaplastic lymphoma kinase (ALK)-positive ALCL (ALK^+ ALCL) or ALK-negative ALCL (ALK^- ALCL). Patients lacking clinical history (lost, empty or not recoverable) were excluded. Candidate patients were identified by the investigators in their respective case databases to confirm the original PTCL diagnosis. The original tumour biopsies and the archived histological preparations were transferred anonymously to the central laboratory for review of the initial diagnosis by the expert committee. Data on the information retrieved is shown in Supplementary Materials.

Central review of tumour samples

The expert committee, comprised of three independent referent hematopathologists from different healthcare centres (Socorro M. Rodríguez-Pinilla, Fina Climent and Miguel A. Piris), simultaneously reviewed all PTCL specimens at the Pathology Department of the Hospital Universitario Fundación Jiménez Díaz (Madrid, Spain) and re-classified or updated them into subtypes according to the WHO 2016 criteria.[4] Immunohistochemical staining procedures are described in Supplementary Materials. For the present study, we selected patients reclassified in one of the following categories: (i) PTCL-NOS, (ii) AITL and (iii) nodal PTCL with a TFH phenotype.[23,24] Diagnosis of nodal PTCL with a TFH phenotype was based on lacking of typical AITL features, such as polymorphous histology, follicular dendritic cell hyperplasia, increase in epithelioid venules, together with the positive expression (≥10%) of at least two TFH markers[9] among the following: PD1, BCL6, CD10 and ICOS. CD30 was considered positive with expression in ≥10% tumour cells while the intensity of staining was estimated visually and scored as no expression (negative), weak, moderate and strong.

Statistical analysis

Categorical variables were reported as percentages and analysed using binomial regression. Continuous variables were reported as mean ± standard deviation or median (range). Follow-up was calculated based on overall observation time, on censoring times for surviving patients, and on reserve censoring by Kaplan–Meier curve analysis.[25,26] Time-to-event analyses (overall survival [OS] defined as the duration of patient survival from the time of treatment initiation; Progression-free survival (PFS) defined as the time from treatment initiation until disease progression or death) were performed using the Kaplan–Meier method and the log-rank test. Estimated mean with a 95% confidence interval (95% CI) was used when the median value was not reached. The Cox proportional hazards model allowed the assessment of the potential prognostic covariates for OS and PFS. Univariate and multivariate analyses are reported using hazard ratios (HRs) with 95% CIs. Factors with $p \leq 0.1$ in univariate analyses were included in the multivariate analyses using two approaches: firstly, excluding potential confounding factors that were already included in further variables, i.e., ECOG PS for the IPI score or bone marrow disease for the PIT score and, secondly, by excluding the IPI and PIT scores. Differences were considered statistically significant at $p < 0.05$. All analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 22.0 (SPSS, Inc., IBM Corp.).

RESULTS

Centralized review of tumour samples

A total of 175 archived tumour samples from 175 patients diagnosed with PTCL were reviewed by the expert committee. Overall, 99 were reclassified according to the WHO 2016 diagnostic criteria into one of the following three PTCL subtypes: (i) PTCL-NOS ($n = 21$), (ii) AITL ($n = 55$) and (iii) PTCL-TFH ($n = 23$).

Agreement between local and centralized diagnosis is shown in Table 1. Of the 54 patients with an initial diagnosis of PTCL-NOS, it was confirmed in only 17 of them, while 19 patients were reclassified as PTCL-TFH and 7 as AITL. In contrast, the initial diagnosis of AITL was confirmed in the majority of the samples reviewed, 47 out of 54. All PTCL-TFH cases were positive for ICOS and all but four cases were also positive for PD1. In contrast, only 44% of cases were positive for three TFH markers (Table 2).

13652141, 2023, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bjh.18941 by Cstc Organización Central Om (Oficialia Mayor) (Urici), Wiley Online Library on [26/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 Agreement between local and centralized diagnosis in the overall series ($n = 175$).

	Diagnosis according to centralized review committee (WHO 2016)			
Local diagnosis	**PTCL-NOS ($n = 21$)**	**AITL ($n = 55$)**	**PTCL-TFH ($n = 23$)**	**Other diagnosis ($n = 76$)**
Peripheral T-cell lymphoma, not otherwise specified ($n = 54$), *n* (%)[a]	17 (31.5)	7 (13.0)	19 (35.2)	11 (20.4)
Angioimmunoblastic T-cell lymphoma ($n = 54$), *n* (%)	1 (1.9)	47 (87.0)	2 (3.7)	4 (7.4)
Follicular variant of peripheral T-cell lymphoma ($n = 1$), *n* (%)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Anaplastic large cell lymphoma, ALK-negative ($n = 19$), *n* (%)	2 (10.5)	0 (0.0)	2 (10.5)	15 (78.9)
Not specified ($n = 1$), *n* (%)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other subtypes ($n = 46$), *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	46 (100.0)
Total ($n = 175$), *n* (%)	21 (12.0)	55 (31.4)	23 (13.1)	76 (43.4)

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALK, anaplastic lymphoma kinase; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; PTCL-TFH, nodal peripheral T-cell lymphoma with a T follicular helper phenotype; WHO 2016, the 2016 revision of the World Health Organization classification of lymphoid neoplasms.

[a]Percentage calculated with respect to the total number of patients for whom data about centralized expert review were available.

TABLE 2 Immunohistochemical profile of patients with PTCL-TFH phenotype ($n = 23$).

Case number	CD3	CD4	ICOS	PD1	CD10	BCL6	EBER
1	Positive	Positive	Positive	Positive	Negative	Positive	Negative
2	Positive	Positive	Positive	Negative	Negative	Positive	Positive
3	Positive	Positive	Positive	Positive	Negative	Positive	Negative
4	Positive	Positive	Positive	Positive	Negative	Negative	Negative
5	Positive	Positive	Positive	Positive	Negative	Negative	Positive
6	Positive	Positive	Positive	Positive	Negative	Positive	Negative
7	Positive	Positive	Positive	Negative	Positive	Positive	Negative
8	Positive	Positive	Positive	Positive	Negative	Positive	Negative
9	Positive	Positive	Positive	Positive	Negative	Positive	Positive
10	Positive	Positive	Positive	Negative	Positive	Negative	Negative
11	Positive	Positive	Positive	Positive	Negative	Negative	Positive
12	Positive	Positive	Positive	Positive	Negative	Negative	Negative
13	Positive	Positive	Positive	Positive	Negative	Positive	Negative
14	Positive	Positive	Positive	Positive	Negative	Negative	Negative
15	Positive	Positive	Positive	Positive	Negative	Negative	Positive
16	Positive	Positive	Positive	Positive	Negative	Negative	Positive
17	Positive	Positive	Positive	Positive	Positive	Negative	Negative
18	Positive	Positive	Positive	Positive	Negative	Negative	Negative
19	Positive	Positive	Positive	Positive	Positive	Negative	Negative
20	Positive	Positive	Positive	Positive	Positive	Positive	Positive
21	Positive	Positive	Positive	Positive	Negative	Negative	Positive
22	Positive	Positive	Positive	Positive	Negative	Negative	Negative
23	Positive	Positive	Positive	Negative	Positive	Negative	Negative

Note: Markers were considered positive with expression in ≥10% of tumour cells.

Abbreviation: PTCL-TFH, nodal peripheral T-cell lymphoma with a T follicular helper phenotype.

Patients

Baseline patient characteristics are shown in Table 3 for the whole study population and in Table 4 for patients with PTCL-TFH. Patients diagnosed with PTCL-TFH were younger than patients with PTCL-NOS and AITL. In addition, patients with PTCL-TFH had a lower-risk profile of baseline characteristics than those diagnosed with PTCL-NOS or AITL: fewer patients with PTCL-TFH presented with advanced stage (Ann Arbor classification) or ECOG

13652141, 2023, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bjh.18941 by Csic Organización Central Om (Oficialia Mayor) (Urici), Wiley Online Library on [26/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 3 Patient baseline characteristics and treatments received.

Characteristics	PTCL-NOS ($n=21$)	AITL ($n=55$)	PTCL-TFH ($n=23$)	Total ($n=99$)	p-Value
Age, median (range)	73.5 (41.6–89.5)	75.4 (38.2–94.1)	61.4 (33.7–81.8)	72.1 (33.7–94.1)	0.003[a]
Sex, male, *n* (%)	14 (66.7)	34 (61.8)	14 (60.9)	62 (62.6)	0.908[b]
Ann Arbor stage, *n* (%)					
I–II	3 (14.3)	6 (10.9)	6 (26.1)	15 (15.2)	0.149[b]
III–IV	18 (85.7)	48 (87.3)	15 (65.2)	81 (81.8)	
Not available/unknown	0 (0.0)	1 (1.8)	2 (8.7)	3 (3.0)	
ECOG 2–4, *n* (%)	4 (26.7)	19 (47.5)	1 (6.3)	24 (33.8)	0.007[c]
CD30 expression, median (range)	5.0 (0.0–90.0)	10.0 (1.0–60.0)	5.0 (0.0–100.0)	10.0 (0.0–100.0)	0.206[a]
CD30 expression (≥1%), *n* (%)	7 (43.8)	31 (62.0)	9 (40.9)	44 (53.4)	0.177[b]
IPI[d], *n* (%)					
Low risk (0–1 points)	2 (25.4)	6 (15.4)	8 (53.3)	16 (23.9)	0.068[c]
Intermediate risk (2–3 points)	6 (46.2)	18 (46.2)	5 (33.3)	29 (43.3)	
High risk (4–5 points)	5 (38.5)	15 (38.5)	2 (13.3)	22 (32.8)	
Total	13 (100.0)	39 (100.0)	15 (100.0)	67 (100.0)	
PIT[d], *n* (%)					
0–1 Adverse factors	4 (30.8)	11 (32.4)	11 (73.3)	26 (41.9)	0.023[c]
2–4 Adverse factors	9 (69.2)	23 (67.6)	4 (26.7)	36 (58.1)	
Total	13 (100.0)	34 (100.0)	15 (100.0)	62 (100.0)	
First-line treatment, *n* (%)					
CHOP or CHOP-like	12 (57.1)	42 (76.4)	17 (73.9)	71 (71.7)	0.592[c]
Others	6 (28.6)[e]	10 (18.2)[f]	5 (21.7)[g]	21 (21.2)	
Did not receive treatment	2 (9.5)	2 (3.6)	1 (4.3)	5 (5.1)	
Not available/unknown	1 (4.8)	1 (1.8)	0 (0.0)	2 (2.0)	
Auto-HSCT, *n* (%)	2 (9.52)	4 (7.27)	9 (39.13)	15 (15.15)	0.004[c]
Allo-HSCT, *n* (%)	0 (0.00)	2 (3.64)	1 (4.35)	3 (3.03)	0.874[c]

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group scale; HSCT, haematopoietic stem cell transplant; IPI, International Prognostic Index; PIT, Prognostic Index for T-cell lymphoma; PTCL, peripheral T cell lymphoma; PTCL-NOS, PTCL not otherwise specified; PTCL TFH, PTCL with a T follicular helper phenotype.

[a]Kruskal–Wallis test.

[b]Chi-square test.

[c]Fisher's exact test.

[d]IPI and PIT were only calculated in those patients with available data for all the analysed variables (i.e. age, disease stage, LDH levels, ECOG and extranodal involvement for IPI; age, performance status, LDH levels, and bone marrow involvement for PIT).

[e]GEMOX (gemcitabine and oxaliplatin) ($n=2$); VMP (bortezomib, melphalan, and prednisone) ($n=1$); SMILE (steroid, methotrexate, ifosfamide, L-asparaginase, and etoposide) ($n=1$); CEP (lomustine, etoposide, and prednisone) ($n=1$); bexarotene + PUVA (psoralen + UVA) + IFN ($n=1$).

[f]CVP (cyclophosphamide, vincristine, and prednisone) ($n=4$); steroids ($n=3$); GEMOX ($n=2$); cyclophosphamide + prednisone ($n=1$).

[g]Cyclophosphamide + prednisone ($n=2$); CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone) + ESHAP (etoposide, cisplatin, methylprednisolone, and cytarabine) ($n=1$); bexarotene + phototherapy ($n=1$); steroids ($n=1$).

2–4. The low-risk profile of PTCL-TFH patients, compared to PTCL-NOS and AITL, was additionally reflected in the IPI and PIT, as shown in Table 2. No significant differences were found between the three PTCL diagnoses in CD30 expression, neither in the median intensity ($p=0.206$) nor in the percentage of CD30 positive cells (≥10%) ($p=0.177$).

Treatment and response to treatment

No significant differences were found between the three groups of patients regarding the first-line treatment received, as shown in Table 3. The majority of patients received CHOP (cyclophosphamide, vincristine, doxorubicin and prednisone) or CHOP-like regimens, regardless of the diagnosis ($p=0.592$). A significantly higher number of patients in the PTCL-TFH group underwent autologous haematopoietic stem cell transplant (auto-HSCT) ($n=9$, 39.1%), compared to PTCL-NOS ($n=2$, 9.5%) and AITL ($n=4$, 7.3%) groups ($p=0.004$), the vast majority in the context of first remission (seven out of nine patients).

Response rates after first-line chemotherapy are shown in Table 5. Complete response rates were lower in the PTCL-NOS subgroup, without however reaching statistical

13652141, 2023, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bjh.18941 by Cstc Organización Central Om (Oficialia Mayor) (Utrc), Wiley Online Library on [26/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 4 Main clinical characteristics and outcomes of patients with PTCL-TFH phenotype ($n = 23$).

Case number	Age (years)	Sex	Ann Arbor stage, *n* (%)	IPI, *n* (%)[a]	First-line treatment	Response	Relapse/progression	Last status
1	57.8	Male	IV	NA/unknown	CHOP (CHOP like)	CR	Yes	Alive
2	45.7	Male	III	NA/unknown	CHOP (CHOP like)	PD	Yes	Death
3	68.6	Male	II	NA/unknown	CHOP (CHOP like)	CR	Yes	Alive
4	62.5	Female	II	Low risk (0–1 points)	CHOP (CHOP like)	CR	Yes	Alive
5	45.4	Female	III	Low risk (0–1 points)	CHOP (CHOP like)	CR	No	Alive
6	33.6	Male	IV	Low-intermediate risk (2 points)	CHOP (CHOP like)	PR	No	Alive
7	50.4	Male	II	Low risk (0–1 points)	CHOP (CHOP like)	CR	No	Alive
8	74.5	Female	IV	Medium-high risk (3 points)	CHOP (CHOP like)	PD	No	Death
9	80.5	Female	III	NA/unknown	Others[b]	PD	NA/unknown	Death
10	81.0	Male	IV	High risk (4–5 points)	Others[b]	PR	Yes	Death
11	59.8	Male	IV	Low risk (0–1 points)	CHOP (CHOP like)	PD	Yes	Death
12	66.5	Male	IV	High risk (4–5 points)	CHOP (CHOP like)	CR	Yes	Alive
13	60.3	Male	IV	NA/unknown	CHOP (CHOP like)	PR	Yes	Death
14	68.2	Female	IV	Medium-high risk (3 points)	Treatment not received	NA/unknown	NA	Lost of follow up
15	35.3	Male	III	Low-intermediate risk (2 points)	Others[c]	NA/unknown	Yes	NA/unknown
16	73.3	Female	IV	NA/unknown	CHOP (CHOP like)	PR	No	Death
17	81.8	Female	NA/unknown	NA/unknown	Others[d]	PR	Yes	Death
18	61.4	Male	IV	Low-intermediate risk (2 points)	CHOP (CHOP like)	PR	No	Death
19	78.8	Female	NA/unknown	NA/unknown	Others[e]	SD	No	Death
20	52.7	Male	IV	Low risk (0–1 points)	CHOP (CHOP like)	SD	No	Alive
21	52.8	Male	I	Low risk (0–1 points)	CHOP (CHOP like)	CR	No	Alive
22	60.6	Female	II	Low risk (0–1 points)	CHOP (CHOP like)	CR	No	Alive
23	66.5	Male	I	Low risk (0–1 points)	CHOP (CHOP like)	CR	No	Alive

Abbreviations: CHOP, cyclophosphamide, vincristine, doxorubicin; CR, Complete Response; ECOG, Eastern Cooperative Oncology Group scale; IPI, International Prognostic Index; NA, not available, PIT, Prognostic Index for T-cell lymphoma; PR, partial response; PD, progression disease; SD, stable disease.

[a]IPI was only calculated in those patients with available data for all the analysed variables (i.e. age, disease stage, LDH levels, ECOG and extranodal involvement).

[b]Cyclophosphamide + prednisone.

[c]CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone) + ESHAP (etoposide, cisplatin, methylprednisolone, and cytarabine).

[d]Steroids.

[e]Bexarotene + phototherapy.

13652141, 2023, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bjh.18941 by Csic Organizacion Central Om (Oficialia Mayor) (Urici), Wiley Online Library on [26/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 5 Response rates after first-line chemotherapy.

Best response, *n* (%)	PTCL-NOS (*n* = 21)	AITL (*n* = 55)	PTCL-TFH (*n* = 23)	Total (*n* = 99)	*p*-Value[a]
Complete response (CR)	2 (9.5)	23 (41.8)	9 (39.1)	34 (34.3)	0.592
Partial response (PR)	7 (33.3)	14 (25.5)	6 (26.1)	27 (27.3)	
Stable disease (SD)	2 (9.5)	5 (9.1)	2 (8.7)	9 (9.1)	
Progressive disease (PD)	5 (23.8)	9 (16.4)	4 (17.4)	18 (18.2)	
Not available/unknown	3 (14.3)	2 (3.6)	1 (4.3)	6 (6.1)	
Not applicable (no first-line treatment)	2 (9.5)	2 (3.6)	1 (4.3)	5 (5.1)	

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; PTCL, peripheral T cell lymphoma; PTCL-NOS, PTCL not otherwise specified; PTCL TFH, PTCL with a T follicular helper phenotype.

[a]Fisher's exact test.

significance, a result probably due to the low number of patients.

Survival

With a median follow-up of 56.07 months (95% CI 38.7–73.4), both PFS and OS estimated by Kaplan–Meier using the reverse censoring method, were significantly higher in patients diagnosed with PTCL-TFH than in those with PTCL-NOS or AITL. The median PFS was 24.6 months (95% CI 15.2–34.1) in patients diagnosed with PTCL-TFH, while it only reached 4.6 (95% CI 1.9–7.3) and 7.8 (95% CI 3.8–11.8) months in patients with PTCL-NOS or AITL, respectively ($p = 0.002$) (Figure 1A). Likewise, a significantly higher median OS was achieved in patients with PTCL-TFH than in the other two groups, 52.6 months (95% CI NE–NE) versus 10.0 (95% CI 0.9–19.2) and 19.3 (95% CI 4.2–34.4) months, respectively ($p < 0.001$) (Figure 1B).

Prognostic factors for survival

Using univariate Cox regression models, it was shown that PTCL-TFH diagnosis was a favourable prognostic factor for PFS and OS compared to PTCL-NOS diagnosis, and there was a positive trend towards better prognosis when compared to AITL. Considering the PFS and OS of patients with PTCL-TFH as the reference category, the HRs for PFS in patients with PTCL-NOS and AITL were 3.2 (95% CI 1.6–6.4, $p = 0.001$) and 1.6 (95% CI 0.8–2.8, $p = 0.158$), respectively, and for OS, 4.7 (95% CI 2.2–3.9, $p < 0.001$) and 1.9 (95% CI 1.0–1.7, $p = 0.069$), respectively. In these univariate analyses, poor PFS or OS were significantly associated with advanced stage disease (stages III–IV according to Ann Arbor classification), number of extranodal sites involved (>1 site), poor performance status (ECOG PS 2–4), increased lactate dehydrogenase levels, and IPI and PIT scores (Tables S2 and S3).

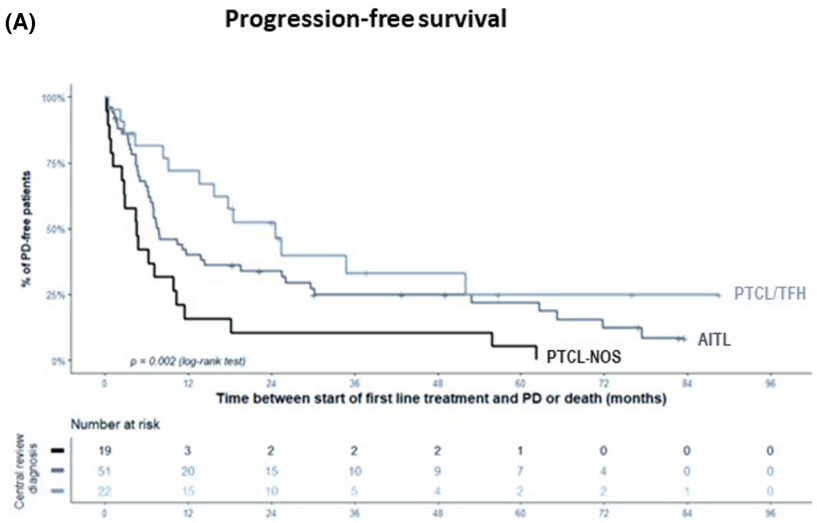
Multivariate Cox regression models revealed that the histological diagnosis maintained its influence on both PFS and OS independently from the IPI considered as an index (shown in Table 6), and from the individual variables of the IPI and PIT (Table S4).

DISCUSSION

It has been recognized that a subset of PTCL cases classified as PTCL-NOS show a TFH cell phenotype, and currently it is recommended to classify them as nodal PTCL-TFH. The inclusion of the new category in the updated WHO 2016 classification has mandated the analysis of TFH-specific marker expression for accurate diagnosis of PTCL, which could be relevant for the management of these patients, particularly in the era of personalized medicine. Due to its low frequency and recent definition, knowledge about the clinical course and prognosis of this new PTCL-TFH category remains limited. To gain insight into its real incidence and characteristics, a cohort of 175 archived tumour samples from patients locally diagnosed with PTCL were centrally reanalysed and eventually reclassified by a committee of experts, following the revised WHO 2016 criteria. Remarkably, we found that up to 68.5% of PTCL-NOS cases were reclassified, 35% as PTCL-TFH and 13% as AITL. Although it is generally accepted that the incidence of PTCL have profound geographic variations,[27] our results suggest an incidence for PTCL-TFH around 45% of all nodal and extranodal PTCL subtypes (excluding cutaneous and leukaemic subtypes).

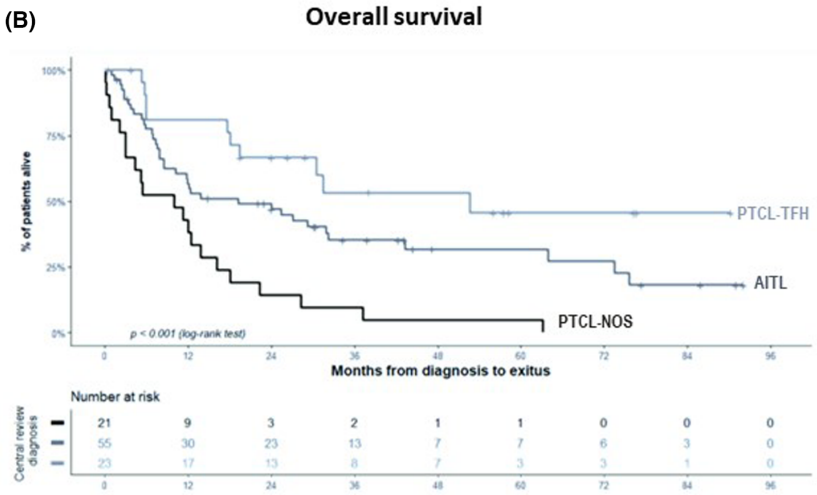
Information on the real incidence of PTCL-TFH is scarce. Recently, Basha et al.[28] reported results from a study evaluating the utility of a panel of TFH markers similar to the ones used in our study (CD10, BCL6, PD-1, CXCL13 and ICOS) for the identification of TFH phenotype in archived samples of AITL ($n = 22$) and PTCL-NOS ($n = 29$) cases. It was shown that, using the minimum WHO 2016 criteria of expression of two TFH markers, as much as 41% of all PTCL-NOS cases (12 out of 29), 56% when analysing only nodal cases (10 out of 18), were reclassified as PTCL-TFH, a percentage similar to that found in our study, although CXCL13 was not included in our panel. However, if the 3-marker benchmark was used, only one case (3%) would be reclassified to PTCL-TFH. Furthermore, if ICOS was excluded from the panel, only 3% and 0% of cases would be reclassified to PTCL-TFH using the 2- and 3-marker threshold, respectively.[28] Similarly, in our series, all PTCL-TFH cases were positive for ICOS and all but four cases were also positive for PD1. In contrast, only 44% of cases were positive for three TFH markers (Table 2). These results highlight the importance of the TFH markers

13652141, 2023, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bjh.18941 by Cstc Organización Central Om (Oficialia Mayor) (Utrc), Wiley Online Library on [26/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License



Progression-free survival (PFS)[1]

	PTCL-NOS (n = 19)	AITL (n = 51)	PTCL-TFH (n = 22)	All (n = 92)	*p*-value[2]
Events, n (%)	19 (100.00%)	42 (82.4%)	14 (63.6%)	75 (81.5%)	0.002
Median PFS, months (95% CI)[1]	4.6 (1.9-7.3)	7.8 (3.8-11.8)	24.6 (15.2-34.1)	9.2 (5.5-13.0)	



Overall survival (OS)[1]

	PTCL-NOS (n = 21)	AITL (n = 55)	PTCL-TFH (n = 23)	All (n = 99)	*p*-value[2]
Events, n (%)	21 (100.00%)	37 (67.3%)	10 (43.5%)	68 (68.7%)	< 0.001
Median OS, months (95% CI)[1]	10.0 (0.9-19.2)	19.3 (4.2-34.4)	52.6 (NE)[3]	18.1 (8.3-27.9)	

FIGURE 1 Progression free survival (A) and overall survival (B) curves. [1]Estimated by Kaplan–Meier using the reverse censoring method; [2]Long-Rank test; [3]95% CI could not be calculated in this group due to the small sample size (mean OS was 53.1 months [95% CI 36.7–69.5]). Analysis performed on patients with available OS data (A) or PFS data (B). AITL, angioimmunoblastic T-cell lymphoma; ALK, anaplastic lymphoma kinase; OS, overall survival; PFS, progression-free survival; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; PTCL-TFH, nodal peripheral T-cell lymphoma with a T follicular helper phenotype.

13652141, 2023, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bjh.18941 by Cstc Organización Central Om (Oficialia Mayor) (Utrci), Wiley Online Library on [26/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 6 Multivariate Cox regression model for PFS and OS.

	PFS ($n=62$)			OS ($n=67$)		
Variable	***N***	**HR for PFS (95% CI)**	***p*-Value**	***N***	**HR for OS (95% CI)**	***p*-Value**
Diagnosis by centralized review committee						
PTCL-TFH[a]	14	-	-	15	-	-
PTCL-NOS	13	4.1 (1.4–11.5)	0.008	13	5.7 (1.7–18.8)	0.004
AITL	35	2.6 (1.0–6.5)	0.047	39	2.6 (0.9–7.7)	0.096
IPI						
Low-intermediate risk (0–1)[a]	15	-	-	16	-	-
Intermediate risk (2–3)	26	1.0 (0.4–2.5)	0.945	29	1.2 (0.4–3.1)	0.748
High risk (4–5)	21	2.7 (1.1–6.5)	0.031	22	3.3 (1.3–8.7)	0.015

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; IPI, International Prognostic Index; OS, overall survival; PFS, progression-free survival; PTCL, peripheral T cell lymphoma; PTCL-NOS, PTCL not otherwise specified; PTCL-TFH, PTCL with a T follicular helper phenotype.

[a]Reference categories.

selected as well as the number of positive markers when diagnosing PTCL. Molecular profiling has been shown to be a useful and applicable tool, beyond the field of this research, in the classification and prognostication of nodal PTCL.[29–31]

Although, in general, T-cell lymphomas have a very poor prognosis,[32,33] the results of our study suggest that patients with PTCL-TFH might have more favourable baseline prognostic features and better outcomes than those with AITL or PTCL-NOS. Compared to the two other groups, they were found to be younger, to have better performance status and commonly have low-risk IPI and PIT scores. Relapse rate after standard first-line chemotherapy was significantly lower among patients with PTCL-TFH, leading to better PFS and OS independent from other prognostic factors. To our knowledge, this finding had not been previously reported.

In fact, very few studies have investigated the clinical differences among the PTCL-TFH, AITL and PTCL-NOS. Suzuki et al.[34] have recently reported in abstract form the results from research conducted in 166 cases of PTCL diagnosed at Kurume University, Japan, including AITL ($n=45$), PTCL-TFH ($n=63$) and PTCL-NOS ($n=58$). In contrast to our results, the Japanese group did not observe significant differences in clinical findings or survival between PTCL subtypes. The diverging conclusions between the two studies must be interpreted with caution since the populations included in the studies might not be entirely comparable. Pronounced differences have been observed in the incidence, proportions of PTCL subtypes and survival between racial/ethnic groups, which may explain, at least in part, these discrepancies.[35–38] Furthermore, unlike the Japanese study, ours is multicentre and includes a centralized review of the histology by an expert committee. In another retrospective study from the LYSA group which included centralized review of 94 AITL and 16 PTCL-TFH cases, Dobay et al.[8] did not find significant differences in clinical features and outcomes between both groups. In contrast, Kurita et al analysed the clinicopathologic features of patients with Lennert lymphoma ($n=26$) and AITL ($n=42$) and found that, as compared with AITL, TFH cell marker-positive Lennert lymphoma was associated with significantly lower frequencies of B symptoms, skin rash and high-intermediate-risk or high-risk IPI values, although the prognosis did not differ significantly between both groups.[39] Given the scarcity of studies carried out in this context, the low number of patients included with PTCL-TFH subtype and the discrepancies in the results, new studies with larger series of patients are needed.

Due to the relatively low incidence of PTCL, high-level evidence from randomized clinical trials or a disease rationale to help define the optimal first-line treatment for these patients is lacking. Instead, therapeutic strategies commonly used in aggressive B-cell lymphomas, such as CHOP or CHOP-like chemotherapy, have been adopted for first-line PTCL treatment, which is associated with a high failure rate and frequent relapses (Refs [40, 41] and references therein). To overcome the dismal outcome seen in this patient population, intensive strategies such as auto-HSCT are frequently used as consolidation of first remission[42–46] although randomized trials are lacking and the precise role of auto-HSCT for PTCLs in front-line settings remains unknown. In our study, significantly more patients in the PTCL-TFH group underwent auto-HSCT, most of them after first remission, more likely reflecting the better treatment responsiveness and more favourable prognostic features of PTCL-TFH compared to the other two relevant subtypes.

Our study has several strengths, the most important of which concerns the centralized review of histologically confirmed PTCL cases by an expert committee and the relatively long clinical follow-up of almost 5 years. However, it has also some limitations such as the retrospective nature of the study and the relatively small sample size that inevitably led to a small number of patients in each diagnostic group. Also, it is important to point out that the Clinical Advisory Committee has recently published the International Consensus Classification of Mature Lymphoid Neoplasms,[47] in which they recommend the use of a 5-marker panel for establishing the

13652141, 2023, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bjh.18941 by Cstc Organización Central Om (Oficialia Mayor) (Utrc), Wiley Online Library on [26/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TFH immunophenotype. Since we used the WHO 2016 classification of lymphoid neoplasms, the expression of at least two phenotypic markers was utilized in our study. Thus, in our re-classification, there is a chance that we are missing some TFH cases that would be probably found if using a 5-marker panel. Another point to consider is that, although there is a trend towards a better prognosis for PTCL-TFH when compared to AITL, no statistically significant differences were found for OS or PFS, probably due to the small sample size. Larger series should be conducted to validate these results. Finally, our study did not include a genetic analysis to help in the characterization of the different PTCL phenotypes. Recently published classifications recognize the importance of gene expression signature and mutation profiles in the characterization of TFH,[47,48] therefore this kind of analysis should be performed in future studies.

In conclusion, our study supports the existence of the PTCL-TFH subtype, with discrete clinical characteristics compared to the PTCL-NOS and AITL subtypes. After reclassifying patients according to the WHO 2016 criteria, we found that patients with PTCL-TFH presented with more favourable prognostic factors as well as improved clinical outcomes, including higher PFS and OS, than patients with either PTCL-NOS or AITL. New studies with larger series should be performed in order to corroborate the findings reported in this study.

AUTHOR CONTRIBUTIONS

Alejandro Martín García-Sancho designed the study, acquired the data and wrote the manuscript, Socorro M. Rodríguez-Pinilla planned the study, acquired the data and wrote the manuscript; Raúl Córdoba planned the study; Eva Domingo-Domenech, Fina Climent, Joaquín Sánchez-Garcia, Javier López Jiménez, Mónica García-Cosío Piqueras, Josep Castellvi, Ana Julia González, Sonia González de Villambrosia, José Gómez Codina, Belén Navarro, Guillermo Rodríguez, Juan José Borrero and Máximo Fraga acquired the data; Lourdes Baeza analysed the data. All authors interpreted the data and approved the final manuscript.

ACKNOWLEDGEMENTS

We want to particularly acknowledge patients and Biobank HUB-ICO-IDIBELL (PT20/00171) integrated with the Spanish Biobank Network and Xarxa Banc de Tumors de Catalunya (XBTC) for their collaboration. The authors received medical writing assistance in the preparation of this manuscript from Luis F. García-Fernández, PhD and Vanessa Marfil, PhD (Medical Statistics Consulting, S.L., Valencia, Spain) supported by funding from Takeda Farmacéutica España, S.A.

FUNDING INFORMATION

This work was supported by Takeda Farmacéutica España, S.A. The authors received no compensation for writing the manuscript.

CONFLICT OF INTEREST STATEMENT

AMG-S has received speaker fees from Roche, Celgene, Janssen, Servier, Gilead, Takeda and Novartis and consulting fees from Roche, Celgene/BMS, Morphosys, Kyowa Kirin, Clinigen, Eusa Pharma, Novartis, Gilead, Servier and Incyte. RC has received speaker fees from Takeda Farmacéutica España, S.A.G. GR has received consultancy fees from Celgene, Janssen, Roche and Takeda. SGdV has received speaker fees from Janssen and Roche. JL-J has received speaker fees from Abbvie, Gilead, Janssen, Merck Sharp & Dohme, Roche and Takeda, and research funding from Abbvie, Gilead, Janssen and Roche. ED-D has received consultancy fees from Takeda, research funding from Bristol-Myers Squibb and Takeda, and financial support for travel, accommodation and meeting expenses from Janssen, Roche and Takeda. MF has received speaker fees from Takeda. AN and LB are employees of Takeda Farmacéutica España S.A. SMR-P, FC, JS-G, MG-CP, JC, AJG, JG-C, BN and JJB declare no conflicts of interest related to this manuscript.

DATA AVAILABILITY STATEMENT

The datasets, including the redacted study protocol, redacted statistical analysis plan and individual participants data supporting the results reported in this article, will be made available from lourdes.baeza@takeda.com within 3 months from the initial request to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization.

ETHICS STATEMENT

The study (TAK-HEM-2015-01) was classified as an Observational Study by the Spanish Agency of Medicines and Health Products (AEMPS) in February 2015 and was approved in April 2015 by an accredited Clinical Research Ethics Committee in Spain, according to the applicable Spanish legislation (Order SAS/3470/2009). The study protocol was approved by the ethics committee of each one of the participating sites.

PATIENT CONSENT STATEMENT

For this study, the Ethics Committee approved a patient information sheet and informed consent. This informed consent was obtained in writing from each patient (alive patients) prior to their participation in the study. The Ethics Committee approves the exemption from obtaining consent, when obtaining such consent is not possible or represents an unreasonable effort (deceased patients), and when encoded data are processed, in accordance with Spanish legislation Order SAS/3470/2009 and Royal Decree 1716/20114.

CLINICAL TRIAL REGISTRATION (INCLUDING TRIAL NUMBER)

This is a subanalysis of the Real-T study.[19]

13652141, 2023, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bjh.18941 by Csic Organización Central Om (Oficialia Mayor) (Urici), Wiley Online Library on [26/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

ORCID

Alejandro Martín García-Sancho https://orcid.org/0000-0001-6330-1028
Raúl Córdoba https://orcid.org/0000-0002-7654-8836

REFERENCES

1. Armitage JO. The aggressive peripheral T-cell lymphomas: 2015. Am J Hematol. 2015;90(7):665–73.
2. Fiore D, Cappelli LV, Broccoli A, Zinzani PL, Chan WC, Inghirami G. Peripheral T cell lymphomas: from the bench to the clinic. Nat Rev Cancer. 2020;20(6):323–42.
3. Van Arnam JS, Lim MS, Elenitoba-Johnson KSJ. Novel insights into the pathogenesis of T-cell lymphomas. Blood. 2018;131(21):2320–30.
4. Swerdlow SH, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J. WHO classification of tumours of haematopoietic and lymphoid tissues. Revised 4th ed. France: IARC Publications; 2017.
5. Fazilleau N, Mark L, McHeyzer-Williams LJ, McHeyzer-Williams MG. Follicular helper T cells: lineage and location. Immunity. 2009;30(3):324–35.
6. Laurent C, Fazilleau N, Brousset P. A novel subset of T-helper cells: follicular T-helper cells and their markers. Haematologica. 2010;95(3):356–8.
7. Kim CH, Lim HW, Kim JR, Rott L, Hillsamer P, Butcher EC. Unique gene expression program of human germinal center T helper cells. Blood. 2004;104(7):1952–60.
8. Dobay MP, Lemonnier F, Missiaglia E, Bastard C, Vallois D, Jais JP, et al. Integrative clinicopathological and molecular analyses of angioimmunoblastic T-cell lymphoma and other nodal lymphomas of follicular helper T-cell origin. Haematologica. 2017;102(4):e148–e51.
9. Piris MA, Rodriguez-Pinilla SM, Santonja C, Betancor I, Alonso-Alonso R, Gru AA, et al. Update on peripheral T-cell lymphomas with T-helper phenotype: are there too many subtypes? Semin Diagn Pathol. 2020;37(1):24–31.
10. Huang Y, Moreau A, Dupuis J, Streubel B, Petit B, Le Gouill S, et al. Peripheral T-cell lymphomas with a follicular growth pattern are derived from follicular helper T cells (TFH) and may show overlapping features with angioimmunoblastic T-cell lymphomas. Am J Surg Pathol. 2009;33(5):682–90.
11. Agostinelli C, Hartmann S, Klapper W, Korkolopoulou P, Righi S, Marafioti T, et al. Peripheral T cell lymphomas with follicular T helper phenotype: a new basket or a distinct entity? Revising Karl Lennert's personal archive. Histopathology. 2011;59(4):679–91.
12. Rodríguez-Pinilla SM, Atienza L, Murillo C, Pérez-Rodríguez A, Montes-Moreno S, Roncador G, et al. Peripheral T-cell lymphoma with follicular T-cell markers. Am J Surg Pathol. 2008;32(12):1787–99.
13. de Leval L, Rickman DS, Thielen C, Reynies A, Huang YL, Delsol G, 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):4952–63.
14. Lemonnier F, Couronné L, Parrens M, Jaïs JP, Travert M, Lamant L, et al. Recurrent TET2 mutations in peripheral T-cell lymphomas correlate with TFH-like features and adverse clinical parameters. Blood. 2012;120(7):1466–9.
15. Palomero T, Couronné L, Khiabanian H, Kim MY, Ambesi-Impiombato A, Perez-Garcia A, et al. Recurrent mutations in epigenetic regulators, RHOA and FYN kinase in peripheral T cell lymphomas. Nat Genet. 2014;46(2):166–70.
16. Sakata-Yanagimoto M, Enami T, Yoshida K, Shiraishi Y, Ishii R, Miyake Y, et al. Somatic RHOA mutation in angioimmunoblastic T cell lymphoma. Nat Genet. 2014;46(2):171–5.
17. Pileri SA. Follicular helper T-cell-related lymphomas. Blood. 2015;126(15):1733–4.
18. Attygalle AD, Cabecadas J, Gaulard P, Jaffe ES, de Jong D, Ko YH, et al. Peripheral T-cell and NK-cell lymphomas and their mimics; taking a step forward - report on the lymphoma workshop of the XVIth meeting of the European Association for Haematopathology and the Society for Hematopathology. Histopathology. 2014;64(2):171–99.
19. Rodriguez-Pinilla SM, Domingo-Domenech E, Climent F, Sanchez J, Perez Seoane C, Lopez Jimenez J, et al. Clinical and pathological characteristics of peripheral T-cell lymphomas in a Spanish population: a retrospective study. Br J Haematol. 2021;192(1):82–99.
20. European Medicines Agency (EMA). The EMA Guidelines on Good Pharmacovigilance Practices (GVP) 2011 [Internet]. [cited 2022 November 22]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf
21. CPMP Working Party on Efficacy of Medicinal Products. The Good Clinical Practice Standards (CPMP/ICH/135/95) [Internet]. 1990. [cited 2022 November 22]. Available from: https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-10/3cc1aen_en.pdf
22. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO classification of tumours of the haematopoietic and lymphoid tissues. Revised 4th ed. France: IARC; 2008.
23. Manso R, González-Rincón J, Rodríguez-Justo M, Roncador G, Gómez S, Sánchez-Beato M, et al. Overlap at the molecular and immunohistochemical levels between angioimmunoblastic T-cell lymphoma and a subgroup of peripheral T-cell lymphomas without specific morphological features. Oncotarget. 2018;9(22):16124–33.
24. de Leval L, Savilo E, Longtine J, Ferry JA, Harris NL. Peripheral T-cell lymphoma with follicular involvement and a CD4+/bcl-6+ phenotype. Am J Surg Pathol. 2001;25(3):395–400.
25. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials. 1996;17(4):343–6.
26. Altman DG, De Stavola BL, Love SB, Stepniewska KA. Review of survival analyses published in cancer journals. Br J Cancer. 1995;72(2):511–8.
27. Vose J, Armitage J, Weisenburger D. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol. 2008;26(25):4124–30.
28. Basha BM, Bryant SC, Rech KL, Feldman AL, Vrana JA, Shi M, et al. Application of a 5 marker panel to the routine diagnosis of peripheral T-cell lymphoma with T-follicular helper phenotype. Am J Surg Pathol. 2019;43(9):1282–90.
29. Piccaluga PP, Fuligni F, De Leo A, Bertuzzi C, Rossi M, Bacci F, et al. Molecular profiling improves classification and prognostication of nodal peripheral T-cell lymphomas: results of a phase III diagnostic accuracy study. J Clin Oncol. 2013;31(24):3019–25.
30. Fanny D, Philippe R, Ahmad A-S, François L, Pierre-Julien V, Virginie F, et al. Defining signatures of peripheral T-cell lymphoma with a targeted 20-marker gene expression profiling assay. Haematologica. 2020;105(6):1582–92.
31. Rodriguez M, Alonso-Alonso R, Tomas-Roca L, Rodriguez-Pinilla SM, Manso-Alonso R, Cereceda L, et al. Peripheral T-cell lymphoma: molecular profiling recognizes subclasses and identifies prognostic markers. Blood Adv. 2021;5(24):5588–98.
32. Ma H, Marchi E, O'Connor OA. The peripheral T-cell lymphomas: an unusual path to cure. Lancet Haematol. 2020;7(10):e765–e71.
33. Zain JM. Aggressive T-cell lymphomas: 2019 updates on diagnosis, risk stratification, and management. Am J Hematol. 2019;94(8):929–46.
34. Suzuki T, Miyoshi H, Yanagida E, Kawamoto K, Yamada K, Takeuchi M, et al. Clinicopathological differences of nodal PTCL with TFH phenotype from AITL and PTCL, NOS, and detection of prognostic marker of nodal PTCL with TFH phenotype. Hematol Oncol. 2019;37(S2):276–7.
35. 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):717–20.
36. Tajima K, Hinuma Y. Epidemiology of HTLV-I/II in Japan and the world. Gann Monogr Cancer Res. 1992;39:129–49.
37. Bellei M, Chiattone CS, Luminari S, Pesce EA, Cabrera ME, de Souza CA, et al. T-cell lymphomas in South America and Europe. Rev Bras Hematol Hemoter. 2012;34(1):42–7.

13652141, 2023, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bjh.18941 by Cstc Organización Central Om (Oficialia Mayor) (Utrc), Wiley Online Library on [26/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

38. Adams SV, Newcomb PA, Shustov AR. Racial patterns of peripheral T-cell lymphoma incidence and survival in the United States. J Clin Oncol. 2016;34(9):963–71.
39. Kurita D, Miyoshi H, Yoshida N, Sasaki Y, Kato S, Niino D, et al. A clinicopathologic study of Lennert lymphoma and possible prognostic factors: the importance of follicular helper T-cell markers and the association with angioimmunoblastic T-cell lymphoma. Am J Surg Pathol. 2016;40(9):1249–60.
40. d'Amore F, Gaulard P, Trumper L, Corradini P, Kim WS, Specht L, et al. Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v108–15.
41. Abouyabis AN, Shenoy PJ, Sinha R, Flowers CR, Lechowicz MJ. A systematic review and meta-analysis of front-line anthracycline-based chemotherapy regimens for peripheral T-cell lymphoma. ISRN Hematol. 2011;2011:623924.
42. Reimer P, Rudiger T, Geissinger E, Weissinger F, Nerl C, Schmitz N, et al. Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: results of a prospective multicenter study. J Clin Oncol. 2009;27(1):106–13.
43. d'Amore F, Relander T, Lauritzsen GF, Jantunen E, Hagberg H, Anderson H, et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol. 2012;30(25):3093–9.
44. Mercadal S, Briones J, Xicoy B, Pedro C, Escoda L, Estany C, 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):958–63.
45. Rodriguez J, Conde E, Gutierrez A, Arranz R, Leon A, Marin J, 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):32–8.
46. Corradini P, Tarella C, Zallio F, Dodero A, Zanni M, Valagussa P, 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.
47. Campo E, Jaffe ES, Cook JR, Quintanilla-Martinez L, Swerdlow SH, Anderson KC, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. Blood. 2022;140(11):1229–53.
48. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms. Leukemia. 2022;36(7):1720–48.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Martín García-Sancho A, Rodríguez-Pinilla SM, Domingo-Domenech E, Climent F, Sánchez-Garcia J, López Jiménez J, et al. Peripheral T-cell lymphoma with a T follicular-helper phenotype: A different entity? Results of the Spanish Real-T study. Br J Haematol. 2023;203(2):182–193. https://doi.org/10.1111/bjh.18941

13652141, 2023, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bjh.18941 by Cstc Organización Central Om (Oficialia Mayor) (Utrc), Wiley Online Library on [26/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License