Supplementary Materials

Supplementary methods

Information retrieval

Data were collected from paper-based patient medical records or electronic records using an electronic data capture system depending on the center. Clinical data included sex, age, relevant clinical history including lactate dehydrogenase levels, Ann Arbor Stage, Eastern Cooperative Oncology Group Performance Status (ECOG PS), presence of extranodal involvement, CD30 expression, International Prognostic Index (IPI), Prognostic Index for T-cell lymphoma (PIT), treatments, and outcomes [complete response, partial response, stable disease or progression of disease].In the case of IPI and PIT, if data for any of the evaluable variables for each index was not available, the value was not calculated (not available/unknown). The response to first-line treatment recorded in the study was defined as the response indicated in the medical records according to the clinical judgment of the treating physician. Imaging tests were not specifically reviewed for this study. In order to calculate progression-free survival (PFS), date of progressive disease (PD) or date of death were recorded, and the latter of these was used to calculate overall survival (OS). The International Non-Hodgkin Lymphoma Prognostic Factors Project system (A Predictive Model for Aggressive Non-Hodgkin's Lymphoma. The New England journal of medicine.1993. 329(14):987-94) and the Intergruppo Italiano Linfomi system (Gallamini A, Stelitano C, Calvi R, Bellei M, Mattei D, Vitolo U, et al. Peripheral T-Cell Lymphoma Unspecified: A New Prognostic Model from a Retrospective Multicentric Clinical Study. Blood. 2004. 103(7):2474-9) were used to calculate the IPI and the PIT, respectively.

Staining procedure

A panel of antibodies were studied in all cases: CD20, CD3, CD23/CD21, PD1, CD30 and in situ hybridization for EBV expression. Further specific markers were chosen considering their morphology and immunophenotype: PAX5, ICOS, CD10, BCL6, GATA3, T-BET, CD4, CD8, TDT, TCRBETA, TCRGAMMA, TIA-1, KI67 and ALK. Immunohistochemical staining was performed in the Fundación Jiménez Díaz pathology department on paraffin-embedded tissue (Supplementary Table S1), Nevertheless, immunohistochemical staining received from sender centers of each case was also

reviewed.

Supplementary Tables

Supplementary Table S1. Antibodies and dilutions used for the immunohistochemical staining

ANTIBODY	CLON	COMPANY (REFERENCE)	DILUTION / TIME
ALK (CD246)	ALK1	DAKO (GA641)	15'
ALK (D5F3)	D5F3	Cell signalling (3633S)	1:50/ 45´
BCL6	PG-B6p	DAKO (GA625)	25'
CD 3-L	Policlonal	DAKO (GA503)	10'
CD10-L	56C6	DAKO (GA648)	45'
CD20cy	L26	DAKO (GA604	20'
CD21	1F8	DAKO (IR608)	20'
CD23-L	DAK-CD23	DAKO (IR781)	17'
CD30-L	Ber-H2	DAKO (IR602)	8'
CD4	4B12	DAKO (IR649)	20'
CD8	C8/144B	DAKO (IR623)	25'
GATA-3	GATA-3(L50-823)	GENNOVA (AP10569CM)	1:50, 40'
HISTOSONDA EBER	DNP probe	VENTANA (760-1209)	
ICOS	SP98	GENNOVA (AP10607)	1/50 /20
Ki67 -L	MIB-1	DAKO (GA506)	20'
PAX5	DAK-Pax5	DAKO (IR650)	15´
PD1	NAT105C	CNIO	1/500 20´
T-BET	MRQ-46	ROCHE (760-4598)	32´
TCR-B	8A3	Genetex (GTX79388)	1:40/ 20´
TCR-G/DELTA	H-41	Santa Cruz (sc-100289)	1:50 30'
TDT	EP266	DAKO (IR093)	30´
TIA 1	TIA-1	GENNOVA (AP10534C)	1:50/40'

CNIO: Centro nacional de investigaciones oncológicas

Supplementary Table S2. Prognostic factors associated with PFS (univariate analysis)

Variables		N	Median PFS[1], months (95% CI)	HR for PFS (95% CI)	*p*-value[2]
Diagnosis by centralized review committee (3 relevant diagnoses)	PTCL-TFH*	22	24.6 (15.2-34.1)	1.0	0.003
	PTCL-NOS	19	4.6 (1.9-7.3)	3.2 (1.6-6.4)	0.001
	AITL	51	7.8 (3.8-11.8)	1.6 (0.8-2.8)	0.158
Stage of disease (Ann Arbor classification)	I-II*	13	77.3 (5.0-149.7)	1.0	0.003
	III-IV	76	7.0 (5.8-8.3)	3.289 (1.5-7.3)	
Number of extranodal sites involved	0-1*	65	11.2 (5.2-17.3)	1.0	0.035
	>1	21	4.5 (0.0-9.7)	1.8 (1.0-3.0)	
ECOG	0-1*	44	14.3 (5.5-23.2)	1.0	0.006
	2-4	22	3.6 (2.5-18.4)	2.3 (1.3-4.0)	
LDH (increased levels)	No*	33	17.8 (8.7-27.0)	1.0	0.026
	Yes	53	7.0 (4.2-9.8)	1.8 (1.1-2.9)	
IPI	Low risk (0-1)*	15	77.3 (5.3-149.3)	1.0	0.001
	Intermediate risk (2-3)	26	11.8 (7.5-16.1)	1.6(0.7-3.6)	0.263
	High risk (4-5)	21	3.6 (1.1-6.2)	4.0 (1.7-9.4)	0.001
PIT	0-1 adverse factors*	24	62.6 (0.0-150.8)	1.0	0.007
	2-4 adverse factors	35	7.8 (3.4-12.2)	2.5 (1.3-4.8)	

Analysis performed on patients with available PFS data * Reference categories; [1] Estimated by Kaplan - Meier using the reverse censoring method; [2] Log-Rank test.

AITL, angioimmunoblastic T-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group Scale; IPI, International Prognostic Index; LDH, lactate dehydrogenase; 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 (TFH) phenotype.

Supplementary Table S3. Prognostic factors associated with OS (univariate analysis)

Variables		N	Median OS[1], months (95% CI)	HR for OS (95% CI)	*p*-value[2]
Diagnosis by centralized review committee (3 relevant diagnoses)	PTCL-TFH*	23	-	1.0	< 0.001
	PTCL-NOS	21	12.9 (6.4-19.4)	4.700 (2.2-3.9)	< 0.001
	AITL	55	35.5 (25.7-45.3)	1.9 (1.0-1.7)	0.069
Stage of disease (Ann Arbor classification)	I-II*	15	-	1.0	0.010
	III-IV	81	12.2 (5.1-19.2)	3.0 (1.3-7.1)	
ECOG	0-1*	47	32.3 (11.2-53.3)	1.0	< 0.001
	2-4	24	7.4 (3.8-11.0)	2.9 (1.6-5.2)	
Age	≤60 yo*		-	1.0	0.147
	>60 yo		18.1 (8.3-27.9)	1.6(0.8-3.2)	
LDH (increased levels)	No*	36	31.9 (9.5-54.3)	1.0	0.002
	Yes	57	10.0 (5.2-14.8)	2.3 (1.3-3.9)	
IPI	Low risk (0-1)*	16	-	1.0	0.001
	Intermediate risk (2-3)	29	29.3 (7.5-51.1)	1.9 (0.8-4.8)	0.162
	High risk (4-5)	22	6.8 (2.7-11.0)	4.8 (1.9-12.0)	< 0.001
PIT	0-1 adverse factors*	26	63.8 (NE-NE)	1.0	0.007
	2-4 adverse factors	36	12.4 (0.0-24.8)	2.7(1.3-5.4)	

Analysis performed on patients with available OS data * Reference categories; [1] Estimated by Kaplan‑Meier using the reverse censoring method; [2] Log-Rank test.

AITL, angioimmunoblastic T-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group Scale; IPI, International Prognostic Index; LDH, lactate dehydrogenase; 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 (TFH) phenotype.

Supplementary Table S4. Multivariate Cox regression model for PFS and OS individual variables of the IPI and PIT scores

		PFS (n=50)			OS (n=53)		
Variable		**N**	**HR for PFS (95% CI)**	***p*-value**	**N**	**HR for OS (95% CI)**	***p*-value**
Age	≤60 yo*	35	-	0.696	38	-	0.058
	>60 yo	15	1.2 (0.5-2.8)		15	2.5 (1.0-6.4)	
Diagnosis by centralized review committee	PTCL-TFH*	13	-	-	14	-	-
	PTCL-NOS	9	5.3(1.4-19.3)	0.012	9	17.258 (3.285-90.679)	< 0.001
	AITL	28	2.3 (0.9-6.3)	0.101	30	(0.883-10.291)	0.078
Stage of disease (Ann Arbor classification)	No	21	-	0.264	11	-	0.683
	Yes	29	1.9 (0.6-5.9)		42	1.3 (0.4-4.2)	
ECOG	0-1*	37	-	0.082	48	-	< 0.001
	2-4	13	2.3 (0. 9-6.1)		5	10.6 (3.3-34.3)	
Bone marrow infiltration at diagnosis, n (%)	No*	33		0.082	36	-	0.287
	Yes	17	2.3 (0.9-5.9)		17	1.701 (0.6-4.5)	
Number of extranodal sites involved	0-1*	40		0.878	20	-	0.312
	>1	10	1.1 (0.4-2.9)		33	1.7 (0.6-4.6)	
LDH (increased levels)	No*	18	-	0.334	20	-	0.689
	Yes	32	0.615 (0.2;1.7)		33	0.8 (0.3-2.4)	

* Reference categories

AITL, angioimmunoblastic T-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group Scale; IPI, International Prognostic Index; LDH, lactate dehydrogenase; 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 (TFH) phenotype.

1. A Predictive Model for Aggressive Non-Hodgkin's Lymphoma. *The New England journal of medicine* (1993) 329(14):987-94. Epub 1993/09/30. doi: 10.1056/nejm199309303291402.
2. Gallamini A, Stelitano C, Calvi R, Bellei M, Mattei D, Vitolo U, et al. Peripheral T-Cell Lymphoma Unspecified (Ptcl-U): A New Prognostic Model from a Retrospective Multicentric Clinical Study. *Blood* (2004) 103(7):2474-9. Epub 2003/12/03. doi: 10.1182/blood-2003-09-3080.