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ORIGINAL ARTICLE

Characteristics and clinical outcomes of patients with ALK-positive anaplastic large cell lymphoma: Report from the prospective international T-cell lymphoma project

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Abstract

The T-cell Lymphoma Project is an international registry prospective study that enrolled patients with newly diagnosed peripheral T-cell and NK-cell lymphomas (PTCL). The main objective was to define the clinical features and outcomes, establishing a robust benchmark for future clinical trials. Seventy-four institutions from 14 countries in North America, South America, Europe, and Asia collected data on patients diagnosed and treated at their respective centers between September 2006 and February 2018. Among 1553 PTCL patients, 131 (8.4% of the total cohort) were confirmed to have anaplastic large cell lymphoma - kinase positive (ALCL, ALK+). The median age of the patients was 39 years (18–84). Sixty-five patients (66%) had advanced-stage disease, although majority (45 patients, 54%) had a

low-risk International Prognostic Index (IPI) score (0–1). Of 97 patients treated with chemotherapy, 97% received anthracycline-containing regimens. The overall response rate was 81%, with 69 patients (70%) achieving complete remission. Estimated OS and PFS at 3 years were 77% (95% CI: 54%–99%) and 68% (95% CI: 46%–90%), respectively, and at 5 years were very similar, 77% of OS (95% CI: 62%–92%) and 64% of PFS (95% CI: 34%–94%). Multivariate analysis for PFS showed advanced stage (hazard ratios [HR]: 4.72, 95% CI: 1.43–23.9, $p = 0.015$), elevated lactate dehidrogenade (LDH) (HR 4.85; 95% CI: 1.73–13.60, $p = 0.001$), and Eastern Cooperative Oncology Group Performance Status scale (ECOG-PS) ≥2 (HR: 5.25; 95% CI: 1.68–16.4, $p = 0.024$). For OS, elevated LDH (HR: 3.77; 95% CI: 1.98–14.17, $p = 0.014$) and ECOG-PS ≥2 (HR: 4.59; 95% CI: 1.46–14.39, $p = 0.004$) were identified. In summary, although the outcome of ALK+ ALCL is superior to that of other PTCLs, it remains sufficiently favorable, given the young median age of the patients. Our results confirm the usefulness of both IPI and Prognostic Index for T-cell Lymphoma (PIT) in identifying groups of patients with different outcomes. Clinical Trials ID: NCT01142674.

KEYWORDS
ALCL ALK+ lymphoma, outcomes, prospective international T-cell lymphoma project, PTCL

1 | INTRODUCTION

Anaplastic large cell lymphoma kinase-positive (ALCL, ALK+) is a distinct lymphoid neoplasm whose malignant cells express CD30 (TNFR8) and carry translocations of anaplastic lymphoma kinase.[1] Stein et al. first described ALCL in 1985, pointing out the pleomorphic anaplastic features of these malignant lymphocytes, along with their cohesive growth pattern, tendency to invade lymph node sinuses, and uniform CD30 expression.[1–3] Most frequently, ALCL carries the t(2; 5) (p23; q35) translocation that fuses the *ALK* gene to the nucleophosmin gene, resulting in aberrant chimeric nuclear NPM-ALK protein expression.[4] ALK fusions lead to deregulated/constitutive expression of chimeric ALK kinase proteins which can be detected by immunohistochemical staining.[2] Multiple ALK translocations involving different partners have been described, leading to numerous ALK chimeras with unique intracellular distributions. These latter ALCL represent less than 15% of all ALCL, ALK+ cases.[5,6] Downstream ALK signaling cascades modulate both anti-apoptotic signals and growth patterns, fostering lymphoma proliferation, and ultimately promoting aggressive clinical behavior.[6] Recent gene expression and comparative genomic hybridization (CGS) studies have demonstrated unique expression patterns, further consolidating ALCL, ALK+ as a unique genetic, histological, and clinical entity.[7–9]

A large retrospective cohort study suggested that ALCL, ALK+ represents approximately 12% of all peripheral T-cell lymphomas (PTCL), translating into an overall relative frequency of 1%–3% among all non-Hodgkin lymphomas.[10] ALCL, ALK+ most often affects young patients (median age: 34 years), and frequently presents with advanced stage and extensive extranodal involvement. The most frequent extranodal sites include the bone, liver, lungs, and gastrointestinal tract. Moreover, most ALCL, ALK+ patients will respond to initial anthracycline-containing regimens, and up to 60%–70% will be cured of their disease after front-line therapy.[11] Savage et. al. also demonstrated that the International Prognostic Index (IPI) could identify high-risk patients with an age cut-off of 45 years.[11,12] Thus, further studies might facilitate a molecular predictive model to identify patients with a high risk of relapse after CHOP-like therapies at the time of diagnosis and might foster alternative approaches in ALCL, ALK– and ALK+.[12–14]

While several studies reported on epidemiology, clinical features, and outcomes of ALCL, ALK+, these analyses were retrospective data collections. Here, we investigated whether data generated in a large prospective study could confirm these findings. The T-cell Lymphoma Project (TCP) is the largest prospective multicentre cohort study conducted in patients with newly diagnosed PTCL. Herein, we report the analysis of demographics, initial clinical characteristics, treatment patterns, and outcomes of patients with ALCL, ALK+ enrolled in the TCP database. To the best of our knowledge, these results are based on the largest prospective cohort of patients with ALCL, ALK+ confirmed with central pathology, and enrolled in numerous institutions across four continents.

2 | METHODS

The T-Cell Project (NCT01142674), sponsored by the International T-Cell Lymphoma Project, was incepted in 2006 and builds on the prospective collection of data from a cohort of 1553 cases of

PTCL and Natural Killer T-cell Lymphoma, representing the largest study to date of these patients. Adult patients with aggressive, mature, nodal, and extra-nodal PTCL subtypes from the WHO 2001 or WHO 2008 were registered at the time of initial diagnosis.[15,16] The study was devised as a prospective collection of information potentially relevant to outline clinical characteristics and outcomes of the more uncommon PTCL subtypes and better define prognosis for the more frequent subtypes of PTCL; that is, PTCL not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma, and ALCL-. Additional eligibility criteria included age ≥18 years, tissue biopsies adequate for diagnosis and classification, as well as availability for centralized review, clinical data, including baseline information on disease localization, and laboratory parameters at staging. Data were collected during front-line treatment, response evaluation at the end of treatment, and updated follow-up for at least 5 years in living patients. The participating institutions were asked to provide information on consecutive series of cases without any selection. Patients who did not receive any treatment were also included. Data collection was performed using a web-based platform via electronic case report forms on a dedicated website (www.tcellproject.org). It adopted appropriate technology to ensure protection during web communications of the clinical data. Data access and management were regulated using passwords with different levels of admittance, provided that subject confidentiality was respected. Data collection and study management were performed at the study trial office in Modena, Italy. Registration was based on a locally established histological diagnosis; a panel of expert hematopathologists was planned to review the diagnosis of all patients enrolled in the study.

The T-Cell Project was conducted in compliance with the Declaration of Helsinki. The study was approved by the appropriate research ethics committee or institutional review board at each participating institution. Each patient provided written informed consent before registering.

2.1 | Endpoint definition

The primary endpoint of the analysis was overall survival (OS), measured from the date of diagnosis until the date of last contact with living patients or death from any cause. The secondary endpoint was the Progression-Free Survival (PFS), defined as the time from diagnosis until the first documentation of disease progression, relapse, or death for any cause.

Conventional response assessments after the first treatment were adapted from the standardized response criteria for non-Hodgkin's lymphoma and recommendations for the revised response criteria for malignant lymphoma.[17]

Other characteristics, such as demographic data, epidemiology, clinical presentation, and treatment options, were included as secondary endpoints.

2.2 | Statistical analysis

Data were analyzed using Fisher's exact test to identify associations between categorical variables. Two-sided p values <0.05 were considered statistically significant. OS and PFS distributions were calculated using the Kaplan–Meier method. Their curves were compared using the log-rank test. To evaluate the influence of different variables on time-to-event outcome variables, Cox regression analyses were performed, and the results were expressed as hazard ratios (HR) with 95% confidence interval. For univariate analysis, variables with $p < 0.05$ were included in the multivariate Cox regression model. Statistical analyses were performed using Stata version 14·2 (StataCorp. LLC), and SPSS v20.0 (IBM Corp.).

3 | RESULTS

In a period of 12 years, between September 2006 and February 2018, 1553 reports were analyzed by the CPT project. They were collected from 74 institutions in 13 countries in Europe, South America, United States of America (USA), and Asia. Most patients (689/1553) were obtained from European sites.

3.1 | Patients' characteristics

Of the 1553 patients registered in the study, a diagnosis of ALCL, ALK+ was centrally confirmed in 131 patients. Patient characteristics are described in Table 1. ALCL ALK+ represented 8.4% of all cases, with similar distribution around the world; except for Asia, where the incidence was 5% (Figure 1). The median age of patients with ALCL, ALK+ patients was 39 years (range, 18–84). Only 13 patients (10%) were aged ≥60 years, and there was a slight male predominance (1:1.5).

Despite most patients (66%) presenting with advanced stage disease, only 16% had high-risk IPI scores. Bone marrow involvement was found in 15%, whereas 7% had bulky disease and extra-nodal involvement was observed in 37%. Despite the missing values, other non-IPI defining high-risk features included elevated C-reactive protein in 72% and 47% of elevated Beta-2 microglobulin. The most common hematologic abnormalities were anemia (Hb < 12 g/dL [37.5%]) and elevated absolute neutrophil count (absolute neutrophil count (ANC) > 6.5 × 10^3/mm^3 [58%]). Thrombocytopenia and leukopenia were uncommon.

3.2 | Treatment characteristics

Data on treatment were available for 99 patients, with two patients receiving the best supportive care only. Majority of the patients (82%, 81/99) received chemotherapy alone, and 10% received combined modality treatments (chemotherapy + radiotherapy). Only 6%

TABLE 1 Clinical characteristics of patients included in the analysis

Parameter	N_{tot}	N (%)
Median follow-up	131	43 months (1–140)
Median age (y)	131	39 years (18–84)
Age ≥60 years	131	13 (10)
Gender (male)	131	78 (60)
ECOG >1	113	25 (22)
B-symptoms	117	69 (59)
Bone marrow involvement	99	15 (15)
Stage I–II	98	33 (34)
Stage III–IV		65 (66)
Extranodal involvement	131	49 (37)
LDH > ULN	111	41 (37)
HB < 12 g/dL	112	42 (37.5)
Platelets <150 K/mm3	111	9 (8)
Bulky disease (>10 cm)	131	9 (7)
Monocyte >800/mm3	103	37 (36)
ANC >6.5 × 103/mm3	109	63 (58)
Beta2-microglubulin > ULN	58	27 (47)
CRP > ULN	57	41 (72)
IPI		
0–1	83	45 (54)
2		25 (30)
3–5		13 (16)
PIT		
0–1	79	64 (81)
2–4		15 (19)
Supportive care only	99	02 (2%)
Chemotherapy alone		81 (82)
Combined CT modality		10 (10)
Radiotherapy alone		-----
Chemotherapy + ASCT		6 (6)
Complete response	99	69 (70)
Partial response		11 (11)
Disease relapsed		17 (17)
Indeterminated response		02 (2)

Abbreviations: ANC, absolute neutrophil count; HB, hemoglobin; LDH, lactate dehidrogenade; ULN, upper limit normal.

of patients received consolidative autologous stem cell transplantation (ASCT) in first remission. Chemotherapy regimen included anthracycline in most of the cases (95%, 94/97), and etoposide was added to intensify treatment in 18% of the cases (18/99). Table 2 describes the chemotherapy regimens by geographic region.

3.3 | Patient outcomes

The overall response rate was 81%, with 70% (69/131) of complete responses. The median follow-up time was 43 months (1–140), and 101 patients (77%) were alive at the time of this study. Twenty-seven (20%) died, and 3 (3%) patients were lost to follow-up. The main causes of death were progressive lymphoma (79%), followed by infection (11%), and solid tumor (4%). Treatment toxicity-related death was reported in 4 cases (3%), and 3% were unknown.

The median OS and PFS for patients with ALK+ ALCL from the entire cohort were not reached. However, OS and PFS estimated in 3 years were 77% (95% CI: 54%–99%) and 68% (95% CI: 46%–90%), respectively. Results estimated in 5 years were very similar at 77% OS (95% CI: 62%–92%) and 64% PFS (95% CI: 34%–94%) (Figure 2).

Patients with localized disease (stage I–II) had higher OS at 87% (95% CI: 77–97) versus advanced stage disease 71% (95% CI: 51%–91%). Meanwhile, PFS was 82% (95% CI: 69%–95%) for localized and 55% (95% CI: 39%–71%) for advanced disease, $p = 0.012$ (Figure 3 A,B).

3.4 | Outcomes in low-versus high-risk disease

Eighty-three patients were stratified using IPI, whereas 79 were stratified using PIT. Forty-six percent of patients were high-risk by IPI (IPI ≥2), and 19% were high risk by PIT (PIT ≥2).

Median PFS was not reached at 5 months for patients with low or high risk according to PIT or IPI (95% CI: 0–48 and 95% CI: 0–49, respectively).

Comparing high-risk versus low-risk patients using both IPI and PIT, high-risk patients had the worst OS (not-reached, estimated at 43% vs. 75% in 5 years), Figure 4.

Most patients (76/99) received anthracycline-based chemotherapy as first-line treatment while another 18% received anthracycline-based chemotherapy combined with etoposide (18/99). Median OS and PFS were not reached when comparing anthracycline and anthracycline/etoposide regimens.

Analyzing the impact of adding etoposide to therapy is not feasible, considering the small sample size of the etoposide group.

Univariate analyses assessed different clinical and laboratory features, and consequently evaluated their impact on OS and PFS (Table 3). Significant predictive values in univariate analysis for OS were ECOG-PS ≥2 ($p = 0.008$), elevated LDH ($p = 0.001$), and Platelets (PTL) > 150 × 10^9 rate ($p = 0.006$). Meanwhile, those for PFS were advanced stage (III-IV) [$p = 0.012$], ECOG-PS ≤2 ($p = 0.005$), elevated LDH ($p = 0.001$), and PTL > 150 × 10^9 rate ($p = 0.007$).

Multivariate analysis for OS identified elevated LDH (HR 3.77, 95% CI: 1.98–14.1, $p = 0.014$) and ECOG-PS ≥2 (HR: 4.59; 95% CI: 1.46–14.3 $p = 0.004$). For PFS, the advanced stage (HR: 4.72; 95% CI: 1.43–23.9, $p = 0.015$), elevated LDH (HR: 4.85; 95% CI: 1.73–13.6, $p = 0.001$), and ECOG-PS ≥2 (HR: 5.25 95% CI: 1.68–16.4, $p = 0.024$).

The effects of the presenting clinical features on PFS and OS are summarized in Table 3.

FIGURE 1 Geographic distribution according to the subtype

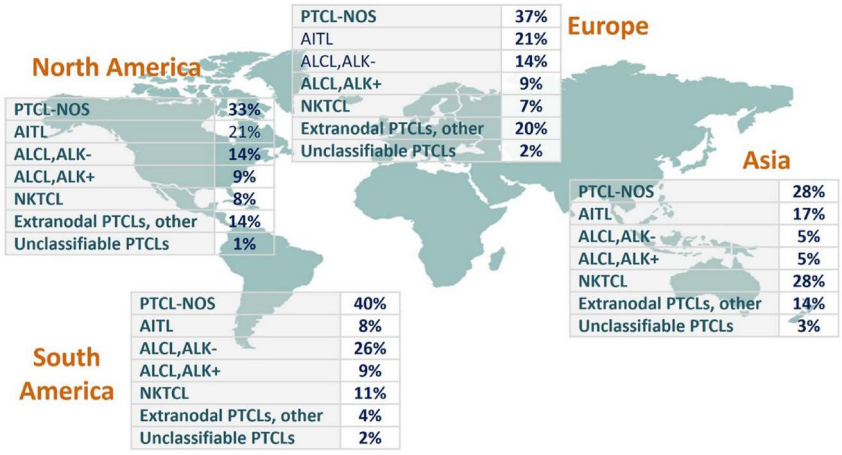

TABLE 2 Chemotherapy regimens between geographic regions

CT regimens	Europe (48) *n* (%)	USA (22) *n* (%)	South America (22) *n* (%)	Asia (7) *n* (%)
Anthracycline	41 (85)	17 (77)	13 (59)	5 (71)
Anthracycline/Etoposide	5 (10)	4 (18)	7 (32)	2 (29)
Etoposide	2 (5)	0 (0)	1 (4.5)	0
Best care therapy	0	1 (5)	1 (4.5)	0

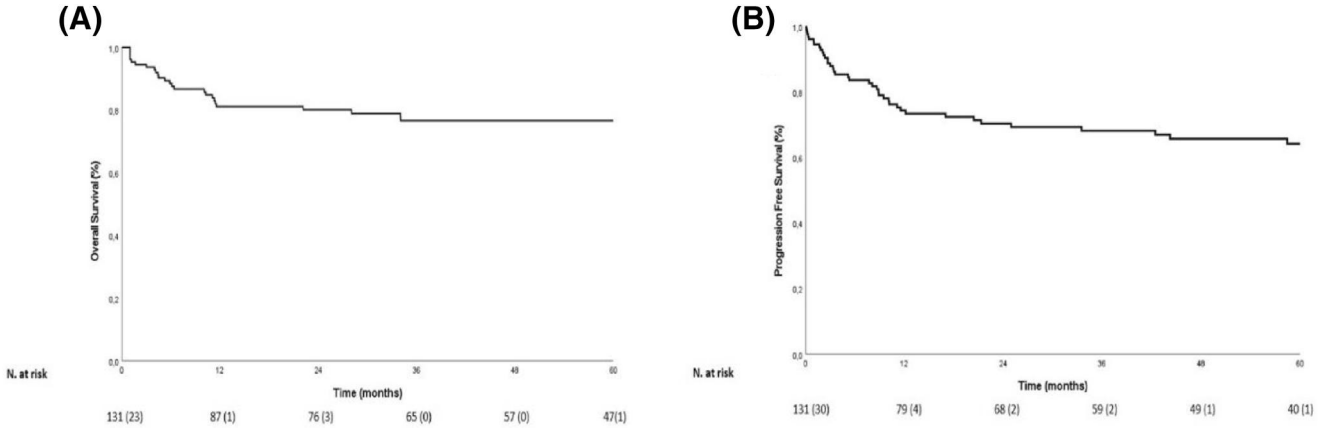

FIGURE 2 (A,B) Overall survival (OS) and Progression-free Survival (PFS) ALCL-ALK+

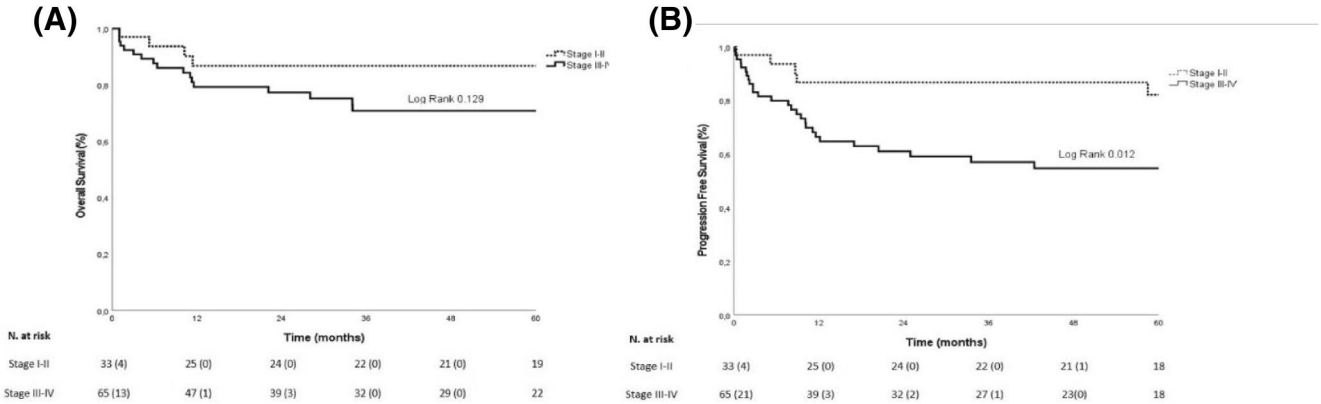

FIGURE 3 (A,B) Overall survival (OS) and Progression-free Survival (PFS) by stages

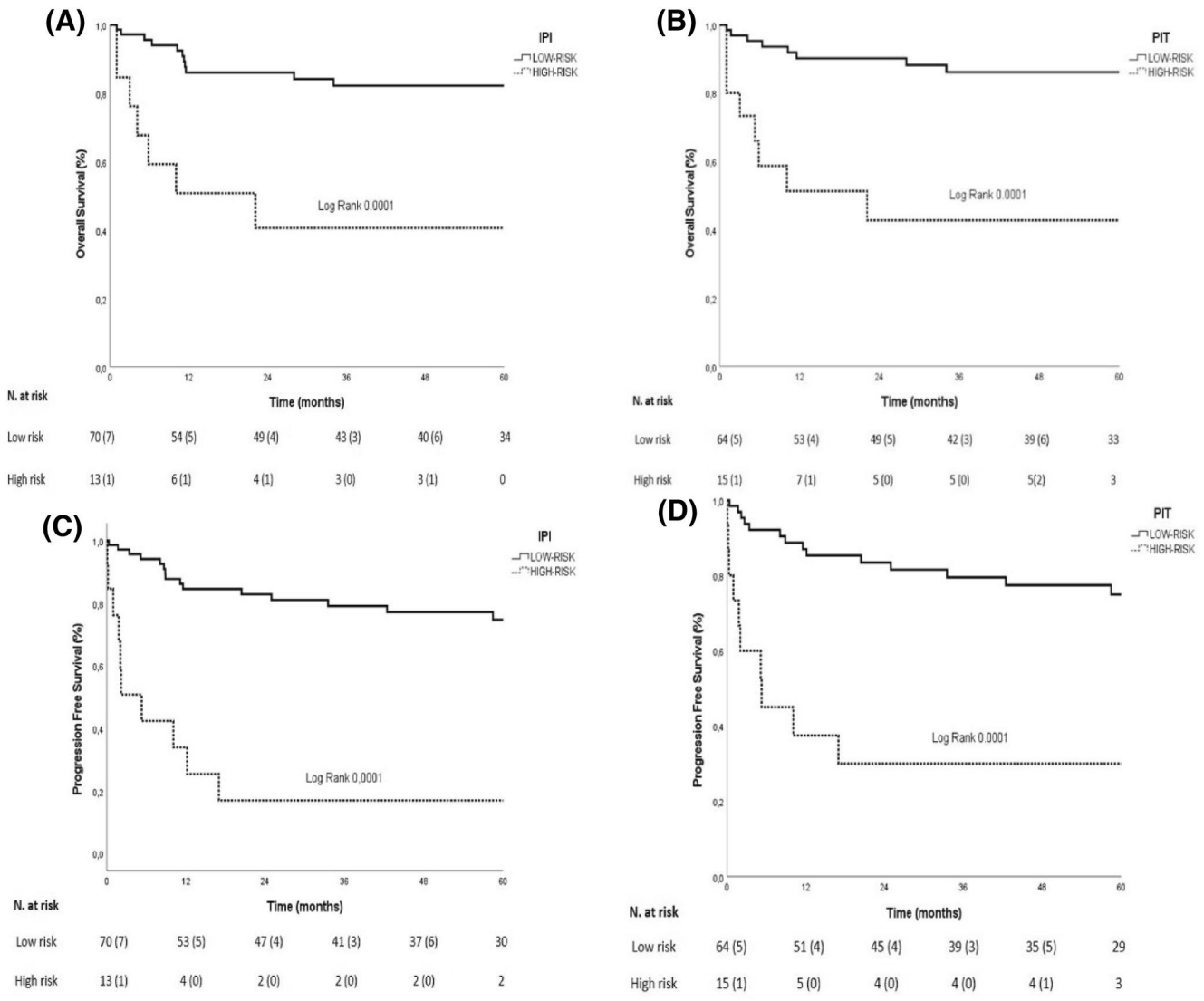

FIGURE 4 (A,B) OS by International Prognostic Index (IPI) and Prognostic Index for T-cell Lymphoma (PIT); (C,D) PFS by IPI and PIT

TABLE 3 Univariate and multivariate analyses

	Univariate analysis		Multivariate analysis			
			OS		PFS	
	OS *p* Value	PFS *p* value	Hazard ratio (95% CI)	*p* Value	Hazard ratio (95% CI)	*p* Value
Stage III/IV	0.129	0.012	-	-	4.72 (1.43–23.9)	0.015
PTL >150 × 10^9	0.006	0.007	-		-	
LDH >normal	0.001	0.001	3.77 (1.98–14.1)	0.014	4.85 (1.73–13.6)	0.001
ECOG PS (≥2)	0.008	0.005	4.59 (1.46–14.3)	0.004	5.25 (1.68–16.4)	0.024

Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group Performance Status scale; LDH, lactate dehidrogenade; PTL, Platelets.

4 | DISCUSSION

ALCL, ALK+ has remained a sufficiently favorable disease for the past 3 decades. In the last edition of the WHO classification, ALCL, ALK+ is recognized as an independent entity within other types of ALCL (ALCL ALK neg, primary cutaneous ALCL, and breast implant-associated ALCL).[1] Compared to other aggressive types of T-cell lymphomas, there is a good tendency to achieve a tumor response with first-line standard treatment; however, ALCL, ALK+ should be identified as a separate disorder from more aggressive types of PTCL.

The results of our prospective study confirmed. The differences in patients with ALCL, ALK+ in age distribution, outcomes, and clinical behavior compared to ALCL, ALK-negative, and PTCL NOS. Several prior studies have also confirmed this higher percentage of young patients (median age, 39 years) and good disease prognosis. We also established a male predominance and high rate of advanced disease stages, as previously reported.[11,12,18]

According to several studies, 70%–90% of patients respond well to anthracycline-based regimens, when approximately 60%–70% of patients are disease-free within 5 years. These data confirmed a favorable outcome for this group of patients. For example, the German High-Grade Non-Hodgkin's Lymphoma Study Group retrospectively analyzed 191 patients with ALCL; among them, 78 patients had ALK + status. Three year OS and EFS were 89.8% and 75.8%, respectively.[12] In 2012, the GELA group presented a retrospective analysis with a long-term follow-up. Here, 138 patients with systemic ALCL were included and 46% had ALCL, ALK+. In this study, the median follow-up duration was 8 years. Results showed that this group of patients had excellent OS and PFS (82% and 72%, respectively).[19]

Despite bright prospects in first-line treatment, up to 30%–40% of ALCL, ALK+ patients undergo relapsed/refractory disease and belong to an unfavorable group. Therefore, we still do not know the specific group of patients who will benefit from improving treatment strategies.

Regarding the consolidation of the first remission, recent data suggest that ASCT remains an option, mostly for high-risk patients.[20,21]

In our analysis, 5 year OS and PFS for patients with advanced-stage ALCL, ALK+ were 75% and 55%, respectively. However, interesting results were obtained after assessing the patients with IPI and PIT. Historically, IPI has been performed for diffuse large B-cell lymphoma, whereas PIT has been proposed for PTCL.[22,23] Our results showed an effective influence of IPI and PIT on risk-group identification. The 5 year OS and PFS in the high-risk IPI and PIT groups were approximately the same (Figure 4A–D) compared to those with more aggressive types, such as PTCL (NOS) or ALCL ALK-negative. These data are comparable with previous results (5 year FFS only 25%–30%).[19] CHOP remains the backbone of the induction regimen for different subtypes of PTCL; therefore, different entities have distinct outcomes. Moreover, based on the current data, we postulate that this regimen is not fully satisfactory for patients with ALCL ALK+ and high-risk IPI or PIT. To this end, adding etoposide (CHOEP) was tested, although there was no benefit in OS with only a slightly improved PFS in young patients, despite high toxicities.[24] In our study, only 18 patients (19%) received etoposide containing regimens; this limited number of patients did not allow us to carry out further significant analyses to evaluate the added value of etoposide. Nevertheless, multiple studies have shown high activity in patients with ALCL ALK+ receiving novel agents targeting CD30 or ALK. The phase 3 ECHELON-II study showed encouraging results for treating patients with CD30-expression PTCL; mainly in systemic ALCL when combining brentuximab-vedotin with CHP (BV+CHP) versus CHOP as first-line, with manageable security, and without excessive toxicities. In this study, 22% of patients were diagnose with ALCL, ALK+. The data showed superior results for OS and PFS in the BV–CHP arm.[25] After a 5 year follow-up, the brentuximab group continued to be superior compared to CHOP, for the ALCL, ALK+ subgroup; the HR was 0.4 (95% CI: 0.17–0.98).[25]

To improve the inferior outcome of ALCL, ALK+, crizotinib, a selective ALK inhibitor, has been introduced, demonstrating a good response value in patients with relapsed/refractory ALCL, ALK +. The downregulation of BCL2 after crizotinib treatment, leading to autophagy and tumor cell death,[26] confirms the ALK experimental models. For this, ALK-driven activation of STAT3 and PI3K signaling supports novel regimens.[27,28] New clinical trials and introducing selective STAT3 degraders are expected to quickly assess new regimens in refractory/relapsed patients[29–31]

Finally, new agents are emerging (i.e., velemetostat, idelalisib, new potent IMIs, STAT3 degraders, etc.), and we expect that their introduction will further increase our arsenal and likely improve patient management.

5 | CONCLUSION

Considering the low incidence of PTCL and its heterogeneity between subgroups, diagnosis and therapeutics remain a challenge. For this reason, huge studies, with high-risk patients is essential to improve our knowledge about this kind of lymphoproliferative diseases.

CHOP-like regimens still remain as the backbone of treating ALCL ALK+, despite its favorable outcomes, up to 30% of patients will need a second line therapy (refractory or relapse patients). This makes it necessary to develop more specific therapies with better long-term response rates, preserving safety profile.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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TRANSPARENT PEER REVIEW

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REFERENCES

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375-2390. https://doi.org/10.1182/blood-2016-01-643569
2. Ferreri AJ, Govi S, Pileri SA, Savage KJ. Anaplastic large cell lymphoma, ALK-positive. *Crit Rev Oncol Hematol*. 2012;83(2):293-302. https://doi.org/10.1016/j.critrevonc.2012.02.005
3. Stein H, Mason DY, Gerdes J, et al. The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. *Blood*. 1985;66(4):848-858. https://doi.org/10.1182/blood.v66.4.848.848
4. Morris SW, Kirstein MN, Valentine MB, et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. *Science*. 1995;267(5196):316-317.
5. Morris SW, Xue L, Ma Z, Kinney MC. Alk+ CD30+ lymphomas: a distinct molecular genetic subtype of non-Hodgkin's lymphoma. *Br J Haematol*. 2001;113(2):275-295. https://doi.org/10.1046/j.1365-2141.2001.02574.x
6. Chiarle R, Martinengo C, Mastini C, et al. The anaplastic lymphoma kinase is an effective oncoantigen for lymphoma vaccination. *Nat Med*. 2008;14(6):676-680. https://doi.org/10.1038/nm1769
7. Iqbal J, Weisenburger DD, Greiner TC, et al. Molecular signatures to improve diagnosis in peripheral T-cell lymphoma and prognostication in angioimmunoblastic T-cell lymphoma. *Blood*. 2010;115(5):1026-1036. https://doi.org/10.1182/blood-2009-06-227579
8. Weisenburger DD, Savage KJ, Harris NL, et al. Peripheral T-cell lymphoma, not otherwise specified: a report of 340 cases from the international peripheral T-cell lymphoma project. *Blood*. 2011;117(12):3402-3408. https://doi.org/10.1182/blood-2010-09-310342
9. 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):323-342. https://doi.org/10.1038/s41568-020-0247-0
10. Vanhentenrijk V, Bempt IV, Dierickx D, Verhoef G, Wlodarska I, De Wolf-Peeters C. Relationship between classic Hodgkin lymphoma and overlapping large cell lymphoma investigated by comparative expressed sequence hybridization expression profiling. *J Pathol*. 2006;210(2):155-162. https://doi.org/10.1002/path.2043
11. Savage KJ, Harris NL, Vose JM, et al. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the international peripheral t-cell lymphoma project. *Blood*. 2008;111(12):5496-5504. https://doi.org/10.1182/blood-2008-01-134270
12. Schmitz N, Trumper 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(18):3418-3425. https://doi.org/10.1182/blood-2010-02-270785
13. Khan N, Ozkaya N, Moskowitz A, Dogan A, Horwitz S. Peripheral T-cell lymphoma - are we making progress? *Best Pract Res Clin Haematol*. 2018;31(3):306-314. https://doi.org/10.1016/j.beha.2018.07.010
14. Xing X, Feldman AL. Anaplastic large cell lymphomas: ALK positive, ALK negative, and primary cutaneous. *Adv Anat Pathol*. 2015;22(1):29-49. https://doi.org/10.1097/pap.0000000000000047
15. Jaffe ESHN, Stein H, Vardiman JW. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues: Pathology and Genetics*. IARC Press; 2001.
16. Swerdlow E, Harris NL, Jaffe ES, et al. *WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues*. IARC Press; 2008.
17. Cheson BD. Staging and response assessment in lymphomas: the new Lugano classification. *Chin Clin Oncol*. 2015;4(1):5.
18. Horwitz S, O'Connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. *Lancet*. 2019;393(10168):229-240.
19. Sibon D, Fournier M, Briere J, et al. Long-term outcome of adults with systemic anaplastic large-cell lymphoma treated within the Groupe d'Etude des Lymphomes de l'Adulte trials. *J Clin Oncol*. 2012;30(32):3939-3946. https://doi.org/10.1200/jco.2012.42.2345
20. Park SI, Horwitz SM, Foss FM, et al. The role of autologous stem cell transplantation in patients with nodal peripheral T-cell lymphomas in first complete remission: report from COMPLETE, a prospective, multicenter cohort study. *Cancer*. 2019;125(9):1507-1517. https://doi.org/10.1002/cncr.31861
21. García-Sancho AM, Bellei M, López-Parra M, et al. Autologous stem cell transplantation as consolidation of first-line chemotherapy in patients with peripheral T-cell lymphoma: a multicenter GELTAMO/FIL study. *Haematologica*. 2022. (in press). https://doi.org/10.3324/haematol.2021.279426
22. Zing NPC, Fischer T, Zain J, Federico M, Rosen ST. Peripheral T-cell lymphomas: incorporating new developments in diagnostics, prognostication, and treatment into clinical practice-PART 1: PTCL-NOS, FTCL, AITL, ALCL. *Oncology*. 2018;32(7):e74-e82.
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(7):2474-2479. https://doi.org/10.1182/blood-2003-09-3080
24. Cederleuf H, Pedersen MB, Jerkeman M, Relander T, d'Amore F, Ellin F. The addition of etoposide to CHOP is associated with improved outcome in ALK+ adult anaplastic large cell lymphoma: a Nordic lymphoma group study. *Br J Haematol*. 2017;178(5):739-746. https://doi.org/10.1111/bjh.14740
25. Horwitz S, O'Connor OA, Pro B, et al. The ECHELON-2 Trial: 5-year results of a randomized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma. *Ann Oncol*. 2022;33(3):288-298. https://doi.org/10.1016/j.annonc.2021.12.002
26. Passerini CG, Farina F, Stasia A, et al. Crizotinib in advanced, chemoresistant anaplastic lymphoma kinase-positive lymphoma patients. *J Natl Cancer Inst*. 2014;106(2):djt378. https://doi.org/10.1093/jnci/djt378
27. Werner MT, Zhang Q, Wasik MA. From pathology to precision medicine in anaplastic large cell lymphoma expressing anaplastic lymphoma kinase (ALK+ ALCL). *Cancers (Basel)*. 2017;9(10):138. https://doi.org/10.3390/cancers9100138
28. Chiarle R, Voena C, Ambrogio C, Piva R, Inghirami G. The anaplastic lymphoma kinase in the pathogenesis of cancer. *Nat Rev Cancer*. 2008;8(1):11-23. https://doi.org/10.1038/nrc2291
29. Astone GCL, Chiu W, Kayembe C, et al. Selective STAT3 degraders dissect peripheral t-cell lymphomas vulnerabilities empowering

personalized regimens. *Blood*. 2021;138((Suppl 1)):865. https://doi.org/10.1182/blood-2021-153995

30. Horwitz SM, Koch R, Porcu P, et al. Activity of the PI3K-delta, gamma inhibitor duvelisib in a phase 1 trial and preclinical models of T-cell lymphoma. *Blood*. 2018;131(8):888-898. https://doi.org/10.1182/blood-2017-08-802470
31. Bai L, Zhou H, Xu R, et al. A potent and selective small-molecule degrader of STAT3 achieves complete tumor regression in vivo. *Cancer Cell*. 2019;36(5):498-511. https://doi.org/10.1016/j.ccell.2019.10.002

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