RESEARCH ARTICLE

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Real-Life Experience Regarding Clinical Characteristics and Treatment Outcome in Non-Cutaneous Peripheral T-Cell Lymphomas: A Multicenter Study of the Turkish Hematology Research and Education Group (ThREG)

Non-kutanöz Periferik T-hücreli Lenfomalarda Klinik Özellikler ve Tedavi Sonuçlarına ilişkin Gerçek Yaşam Deneyimi:Türk Hematoloji Araştırma ve Eğitim Grubunun Çok Merkezli Çalışması

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Abstract

Objective: Peripheral T-cell lymphomas (PTCLs) are an uncommon and quite heterogeneous group of disorders, representing only 10%-15% of all non-Hodgkin lymphomas. Although both molecular and clinical studies have increased in recent years, we still have little knowledge regarding real-life practice with PTCLs. In this study, we aimed to investigate the clinical characteristics and treatment outcomes of a large population-based cohort of patients presenting with systemic non-cutaneous PTCL.

Materials and Methods: We conducted a multicenter retrospective analysis of 190 patients consecutively diagnosed and treated with non-cutaneous PTCLs between 2008 and 2016.

Results: Considering all first-line treatment combinations, the overall response rate was 65.9% with 49.4% complete remission (n=81) and 16.5% partial response (n=27). The 5-year overall survival and event-free survival rates were significantly different between the transplant and non-transplant groups (p<0.01, and p=0.033, respectively).

Conclusion: The retrospective analysis of a large volume of real-life data on the Turkish experience regarding non-cutaneous PTCL patients showed consistent results compared to other unselected PTCL cohorts with some minor differences in terms of survival and transplantation outcomes. The long-term outcome of patients who receive autologous hematopoietic cell transplantation as part of upfront consolidation or salvage therapy is favorable compared to patients who are unable to receive high-dose therapy.

Keywords: Lymphomas, Autologous stem cell transplantation, T-cell lymphomas, Non-Hodgkin lymphoma

Öz

Amaç: Periferik T-hücreli lenfomalar (PTHL) nadir görülen, oldukça heterojen bir grup hastalıktır ve tüm non-Hodgkin lenfomaların sadece %10-15'ini oluşturur. Son yıllarda hem moleküler hem de klinik çalışmalar artmış olsa da PTHL'ler üzerindeki gerçek yaşam verileri hakkında hala çok az bilgiye sahibiz. Bu çalışmada, sistemik, kutanöz olmayan PTHL hastaları içeren geniş popülasyon tabanlı hasta grubunun klinik özellikleri ve tedavi sonuçlarını araştırmayı amaçladık.

Gereç ve Yöntemler: 2008 ve 2016 yılları arasında kutanöz olmayan PTHL tanısı ile tedavi edilen 190 ardışık hastanın geriye dönük analizini gerçekleştirdik.

Bulgular: Tüm birinci basamak tedavi kombinasyonları dikkate alındığında, genel yanıt oranı; tam remisyon (n=81) %49,4 ve kısmi yanıt (n=27) %16,5 olmak üzere %65,9 saptandı. Beş yıllık genel ve olaysız sağkalım oranları, transplant ve transplant olmayan gruplar arasında önemli ölçüde farklıydı (sırasıyla, p<0,01 ve p=0,033).

Sonuç: Kutanöz olmayan PTHL hastalarıyla ilgili geniş geriye dönük gerçek yaşam veri analizini kapsayan Türkiye deneyimi, sağkalım ve transplantasyon sonuçları açısından bazı küçük farklar içerse de seçilmemiş diğer PTHL serileriyle benzer sonuçlar göstermiştir. Planlı veya kurtarma tedavisinin bir parçası olarak otolog hematopoietik hücre transplantasyonu olan hastaların uzun dönem sonuçları, yüksek doz tedavi almayan hastalara kıyasla daha iyiydi.

Anahtar Sözcükler: Lenfomalar, Otolog kök hücre nakli, T-hücreli Lenfomalar, Non-Hodgkin lenfoma

Introduction

Peripheral T-cell lymphomas (PTCLs) are an uncommon and quite heterogeneous group of disorders, representing only 10%-15% of all non-Hodgkin lymphomas (NHLs). The relatively common subtypes are peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITCL), anaplastic large cell lymphoma (ALCL) either with or without the expression of the anaplastic lymphoma kinase (ALK), and enteropathy-associated T-cell lymphoma (EATL) [1].

Although anthracycline-containing CHOP/CHOP-like chemotherapy regimens have been regarded as standard first-line therapies, the prognosis of patients with PTCLs is generally poor compared with that of patients with B-cell NHLs. In a previous registration study from British Columbia, the 5-year overall survival (OS) rate for patients with PTCL-NOS treated primarily with CHOP/CHOP-like regimens was only 35% [2]. In addition, the median OS and progression-free survival (PFS) rates of patients who did not undergo autologous hematopoietic cell transplantation (auto-HCT) after relapse were 5.5 and 3.1, months, respectively [3].

Apart from some subtypes, PTCLs are aggressive in nature with rapid disease progression and poor response to treatment. Molecular studies over the last few years have greatly contributed to our understanding of the pathogenesis of PTCLs. Some of these new molecular findings have been added to the revised edition of the World Health Organization (WHO) classification of 2016 as they refine both classification and diagnostic criteria [4].

Although both molecular and clinical studies have been increasing in recent years, we still have little knowledge concerning real-life practice with PTCLs. In this study, we aimed to investigate the clinical characteristics and treatment outcomes of a large population-based cohort of systemic non-cutaneous PTCL patients.

Materials and Methods

We conducted a multicenter retrospective analysis of 190 patients consecutively diagnosed and treated with non-cutaneous PTCLs between 2008 and 2016, who had at least the minimal required essential data in their medical records. A tissue biopsy was performed for all patients for diagnostic purposes; all cases were pathologically confirmed by pathologists and classified in accordance with the 2008 WHO classification of hematological malignancies. At the time of diagnosis, the staging workup included medical/

family history, physical examination, complete blood count, liver function tests, renal profile, and computed tomography (CT) or fluorodeoxyglucose-positron emission tomography/CT (FDG-PET/CT) scans of the neck, chest, abdomen, and pelvis. Bone marrow biopsy was performed for all patients. The Ann Arbor Staging System was used for staging. Bulky disease was considered when lymph nodes were 10 cm or more in size, or when the mediastinal mass occupied more than one-third of the chest diameter on imaging studies. Results were analyzed in terms of the clinical characteristics and laboratory parameters at diagnosis and response to different treatment regimens. All patients started on treatment were evaluated for response and outcome.

The study was conducted according to 1964 Declaration of Helsinki. All patients gave written informed consent at the time of hospital admission and before any diagnostic evaluation, invasive procedures, or chemotherapy in line with the standard policies of the participating centers.

Statistical Analysis

Data were collected regarding patients' age at diagnosis, date of diagnosis, histopathology findings, stage, International Prognostic Index (IPI) score, details regarding response to first-line therapy, duration of response, last follow-up, and date of death. Due to the retrospective design of the study, we were unable to acquire all relevant information regarding the management of patients throughout the course of the disease. Data regarding response to second and further lines of chemotherapy and indications for auto-HCT were not available for analysis. Responses were evaluated and reported by the treating physician. Complete response was defined as the resolution of clinically apparent lymphadenopathy and radiographic complete response was established using CT and/or FDG-PET/CT. PFS was defined as the time from initiation of therapy to the time of documented progression, death, or last follow-up. Descriptive statistics were used for baseline patient characteristics. OS was calculated from the date of the start of treatment to the date of death or loss to follow-up. Kaplan-Meier analysis was performed using SPSS 19 (IBM Corp., Armonk, NY, USA) and statistical significance was verified using the log-rank test. Values of $p<0.05$ were accepted as statistically significant.

Results

Patients and Disease Characteristics

The patient characteristics of our cohort are detailed in Table 1. A total of 190 patients were enrolled and analyzed within the study period. The group of patients included 63 women and 127 men whose median age at the initiation of therapy was 54.0 (19-79) years. According to the WHO classification, PTCL-NOS was the most common histological subtype (43.2%), followed by ALCL (32.1%). According to Ann Arbor staging, most of the patients (69.8%) had advanced-stage disease (III-IV). On the other hand, most patients had good performance status with 83.4% having Eastern Cooperative Oncology Group performance status of ≤2, but half of the patients had high-intermediate/high-risk disease according to IPI scores.

Treatment Regimens, Responses, and Outcomes

Treatment regimens and patient responses are summarized in Table 2. The majority of patients (n: 168; 92.3%) were treated

Table 1. Patient characteristics.

Characteristics	Number (%)
Age, years (n: 190)	
Median (range)	54.0 (19-79)
Sex (n: 190)	
Female	63 (33.2)
Male	127 (66.8)
Diagnosis (n: 190)	
PTCL-NOS	82 (43.2)
ALK+ ALCL	19 (10.0)
ALK- ALCL	42 (22.1)
AITCL	24 (12.6)
Extranodal NK/T-cell lymphoma, nasal type	15 (7.9)
Enteropathy-associated T-cell lymphoma	5 (2.6)
Others	3 (1.6)
Ann Arbor staging (n: 182)	
1	19 (10.4)
2	36 (19.8)
3	51 (28.0)
4	76 (41.8)
ECOG performance status (n: 163)	
0	37 (22.7)
1	60 (36.8)
2	39 (23.9)
3	20 (12.3)
4	7 (4.3)
IPI (n: 151)	
Low	40 (26.5)
Low-intermediate	38 (25.2)
High-intermediate	36 (23.8)
High	37 (24.5)
Bulky disease (n: 180)	
Absent	163 (90.6)
Present	17 (9.4)

PTCL-NOS: Peripheral T-cell lymphoma not otherwise specified; ALK: anaplastic lymphoma kinase; ALCL: anaplastic large cell lymphoma; ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic Index.

with CHOP or CHOP-like regimens as initial therapy. Fifty-five patients underwent consolidation with upfront auto-HCT after the first achievement of CR. Fourteen patients (7.7%) were treated with other types of chemotherapy regimens. Of these patients, 9, 3, 1, and 1 received hyper-CVAD, SMILE, DEVIC, and DHAP regimens, respectively. Data regarding treatment lines of the study cohort were available for 182 patients. At the time of study entry, 98 (53.9%), 48 (26.4%), 17 (9.3%), and 19 (10.4%) patients had received first-line, second-line, third-line, and fourth-line therapy or beyond, respectively. The median follow-up of the surviving patients was 13.3 (1-91) months.

Considering all first-line treatment combinations, the overall response rate (ORR) was 65.9% with 49.4% complete remission (CR) (n=81) and 16.5% partial response (PR) (n=27). Median PFS and median OS were 6.7 and 28.8 months, respectively (Figure 1). The type of first-line chemotherapy did not have any impact on OS (p=0.207). We also analyzed the effect of induction regimens in terms of intensity. The OS of patients who received CHOP, intensive therapies (EPOCH, DHAP, SMILE, hyper-CVAD), or others (patients who received neither CHOP nor any other type of intensive regimen) were similar (p=0.35).

Median PFS and OS data for each histological subtype are detailed in Table 3. There was no statistically significant difference among histological subtypes of PTCLs regarding PFS (p=0.551) and OS (p=0.241) regardless of whether we treated ALK+ and ALK- ALCL as one entity (ALCL) or evaluated them separately (data not shown) (Figure 2).

Fifty-seven (30%) patients proceeded to transplantation either as upfront consolidation (n=51) or after the first CR (n=6). Due to the limited number of patients who received auto-HCT as salvage therapy, we treated all patients who underwent auto-HCT as a uniform group. The median PFS (8.9 vs. 5.8 months; p=0.033) and OS (48.6 vs. 18.1 months; p<0.01) rates were

Table 2. Treatment regimens and response to treatment.

First-line treatment regimens (n: 182)	Number (%)
CHOP-like regimens	168 (92.3)
CHOP	127 (69.8)
CHOEP	23 (12.6)
CVP	7 (3.8)
COEP	7 (3.8)
EPOCH	4 (2.2)
Others	14 (7.7)
Hyper-CVAD	9 (5.0)
SMILE	3 (1.7)
DEVIC	1 (0.5)
DHAP	1 (0.5)
Response to treatment (n: 164)	
CR	81 (49.4)
PR	27 (14.8)
SD	16 (9.8)
PD	40 (24.4)
Auto-HCT (n: 190)	
Yes	57 (30.0)
PTCL-NOS	29
ALK+ ALCL	1
ALK- ALCL	10
AITCL	9
Extranodal NK/T-cell lymphoma	6
Enteropathy-associated T-cell lymphoma	1
Other	1
No	133 (70.0)

CR: Complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; Auto-HCT: autologous hematopoietic cell transplantation; PTCL-NOS: peripheral T-cell lymphoma not otherwise specified; ALK: anaplastic lymphoma kinase; ALCL: anaplastic large cell lymphoma; AITCL: angioimmunoblastic T-cell lymphoma.

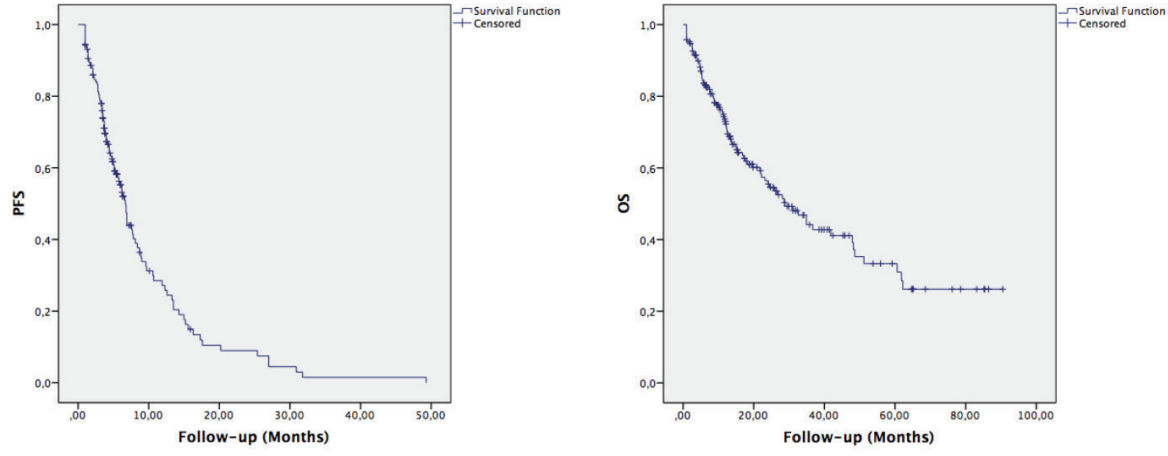

Figure 1. Five-year progression-free survival (PFS) and overall survival (OS) rates for all patients.

significantly superior in patients who underwent auto-HCT compared to patients who did not (Figure 3). The favorable impact of auto-HCT on survival outcomes was independent of risk factors at the time of diagnosis such as Ann Arbor stage, performance status, or extranodal disease (data not shown).

Bulky disease (p<0.001) and high IPI score (p<0.001) were significantly associated with poor OS, but the presence of B symptoms at the time of diagnosis did not have any impact on OS (p=0.614).

Table 3. Median overall survival and progression-free survival according to histological subtypes.

Histologic subtype	Median OS (95% CI) (months)	Log-rank test p	Median PFS (95% CI) (months)	Log-rank test p
ALCL	Not reached	0.241	6.9 (3.9-9.9)	0.551
PTCL-NOS	32.6 (22.0-43.3)		6.6 (5.2-8.0)	
Other	22 (14.3-29.7)		5.9 (3.7-8.1)	

OS: Overall survival; CI: confidence interval; PFS: progression-free survival; ALCL: anaplastic large cell lymphoma; PTCL-NOS: peripheral T-cell lymphoma not otherwise specified.

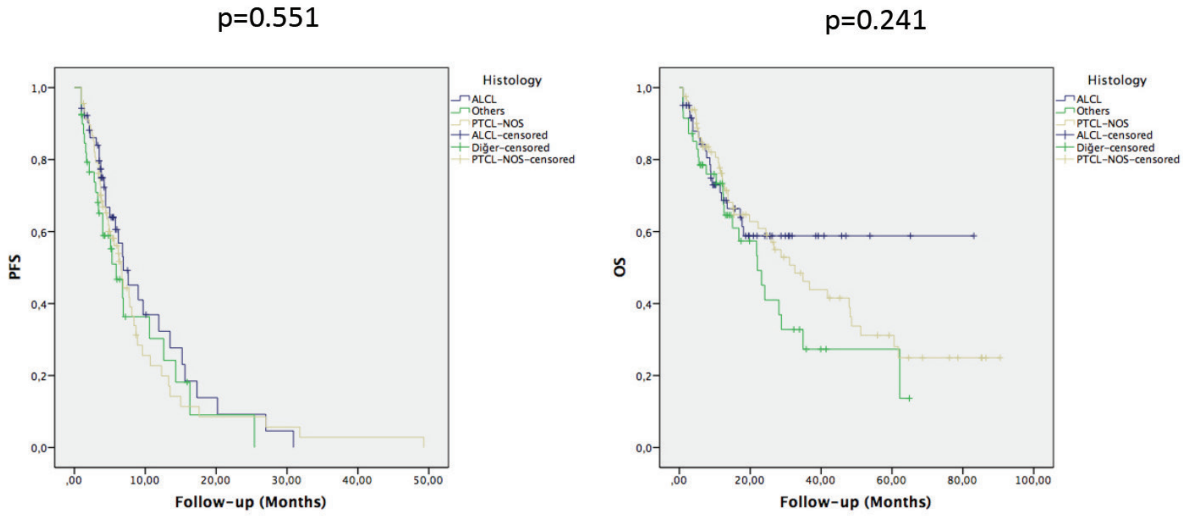

Figure 2. Five-year progression-free survival (PFS) and overall survival (OS) rates according to histological subtypes.
ALCL: Anaplastic large cell lymphoma; PTCL-NOS: peripheral T-cell lymphoma not otherwise specified.

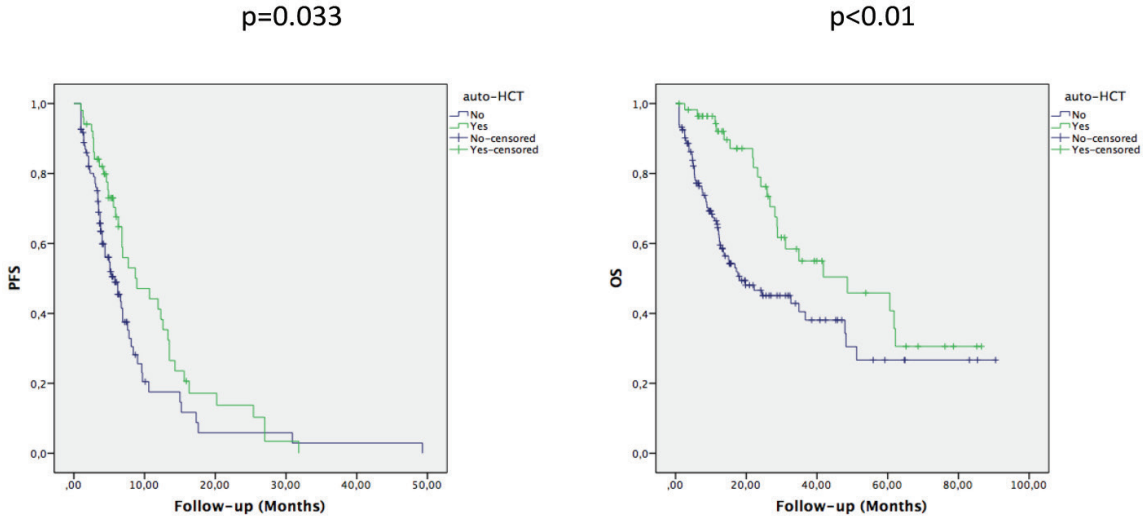

Figure 3. Five-year progression-free survival (PFS) and overall survival (OS) in the transplant and non-transplant groups.
Auto-HCT: Autologous hematopoietic cell transplantation.

Discussion

PTCLs constitute an uncommon group of all lymphomas that show distinct racial and epidemiological variations and are generally associated with poor prognosis compared to their B-cell counterparts. Molecular and clinical studies have increased in recent years, leading to the development of new targeted therapies. However, standard conventional therapies such as CHOP and CHOP-like regimens are still used in first-line protocols, and we have little knowledge about the clinical characteristics and treatment results of PTCL patients who are treated off-study [5]. Therefore, our report reflects the Turkish experience regarding data about PTCLs in a homogeneous population of Caucasian individuals in routine practice.

In our results concerning the particular PTCL histological subtypes, the proportions of PTCL-NOS (43.2%) and ALCL (32.1%) were much higher compared to the results of datasets from the United States and Europe (Swedish, Danish, and Czech data), possibly due to epidemiological diversity [6,7,8,9,10]. Although all samples were directly reviewed by experienced hematopathologists in the centers participating in the present study, the lack of central pathology review may have had an impact on the diagnostic classification of the study cohort. There is also the considerable limitation of immunohistochemical and morphological T-lymphoproliferation diagnostics, and we should bear in mind that the classification of PTCLs is an evolving field. Recent studies have highlighted the importance of molecular genetics and gene-expression profiling in the classification and prognosis of PTCLs [11,12,13]. Two studies clearly showed that the OS of ALK- ALCL patients with *DUSP22* rearrangement demonstrated by fluorescence in situ hybridization was similar to that of ALK+ cases with 5-year OS being 85%-90% [12,13]. Therefore, it is quite possible that at least some of our patients diagnosed with PTCL-NOS would be reclassified into other subtypes by molecular signatures [10,11]. New insights into the pathology of PTCLs will help improve the differentiation of lymphoma subtypes [14].

According to published data, the present ORR (65.9%) and CR (49.4%) rates and median OS (28.8 months) are similar for all PTCL patients, while the median PFS (6.7 months) obtained here is lower compared to the rates in other published series [7,10,15,16]. This may be due to the high percentage of patients with advanced stages and high-risk features, or it may be due to the inability to clearly determine the molecular properties that can influence the prognosis. The addition of etoposide to CHOP (CHOEP) as first-line treatment is beneficial in younger (<60 years) ALK+ ALCL patients, but the outcomes of patients with ALK- ALCL, AITCL, and PTCL-NOS and higher IPI scores are disappointing [17]. The poor PFS of the present study cohort seems to be associated with the relatively limited number (26.5%) of patients in the low-risk IPI group.

In our cohort, we also confirmed a higher proportion of long-term survivors with ALCL compared to other PTCL subtypes. Data from the Swedish Lymphoma Registry concerning 219 cases of ALCL revealed 5-year OS rates of 79% and 38% and 5-year PFS rates of 63% and 31% for ALK+ and ALK- cases, respectively [8,18]. On the other hand, we could not clearly determine the survival of ALCL+ and ALCL- patients due to the small number of ALCL cases, which is a limitation of our study.

The benefits of auto-HCT as upfront consolidation in the treatment of PTCLs are still being debated due to the relatively limited number of randomized trials and the heterogeneity of the disease. Prospective data indicate that long-term outcomes of ALK+ ALCL patients who receive upfront auto-HCT are encouraging, with 63% OS at 10 years compared to patients with other PTCL subtypes (21%) [19]. Long-term results of the NORDIC prospective study of previously untreated patients with PTCLs who received CHOEP induction and upfront auto-HCT as consolidation showed 41% OS at 10 years in the intent-to-treat population [20,21]. Recent recommendations based on the published results of non-randomized studies support the use of first-line auto-HCT in patients with PTCLs, with the exception of ALK+ ALCL [22,23]. Due to the retrospective design of this study, we were unable to get information regarding indications for auto-HCT and factors affecting post-transplant outcomes. Therefore, we do not know why most of the patients did not receive auto-HCT as upfront consolidation. Auto-HCT is also an effective treatment modality as second-line consolidation, especially for patients who achieve CR/PR with salvage chemotherapy. The 5-year OS of PTCL patients who underwent auto-HCT in the second-line setting was reported to be 40%-45% [24,25]. The incorporation of novel drugs including but not limited to brentuximab vedotin, belinostat, and romidepsin in the treatment armamentarium of PTCLs may change the impact of auto-HCT on the long-term outcomes of patients.

An international cohort study including 775 newly diagnosed PTCL patients showed poor outcomes of patients with primary refractory disease or short PFS (<24 months) after first-line treatment. The prognosis of these patients was very poor with only 5 months of median OS [25]. Although our study cohort included PTCL patients at different stages of disease, 80.2% of patients had received first- or second-line therapy at the time of inclusion. A median PFS of 6.7 months and 48.3% of the patients having high-risk IPI scores indicate that we included relatively high-risk PTCL patients in our study cohort. Therefore, we speculate that auto-HCT may overcome the poor prognosis of high-risk PTCL patients.

Lack of central pathology review and a retrospective design are the important limitations of this study. Another shortcoming of the study is that our database did not capture relevant data

regarding salvage treatment regimens in cases of relapsed/refractory disease and the impact of radiotherapy or novel agents like brentuximab on outcome parameters. Although we included 190 patients, cases of the specific WHO-defined PTCL subtypes were relatively limited. We were unaware of the motivations for proceeding to auto-HCT on a case-by-case basis. The decision to perform auto-HCT may be related to the treatment policy of the center, patient preferences, contraindications to transplant, or combinations thereof. On the other hand, we are aware that the pathological subclassification of patients may change based on the 2016 WHO classification instead of the older 2008 version.

Conclusion

Our retrospective real-life data analysis showed consistent results compared to other unselected PTCL cohorts, with some minor differences in terms of survival (PFS with first-line treatment) and transplantation outcomes. A substantial problem remains with the low efficacy of induction (CHOP or CHOP-like) regimens for high-risk and advanced-stage PTCL patients. Auto-HCT may overcome some poor prognostic markers of PTCL like high-intermediate/high-risk IPI and short PFS. Prospective, multinational, randomized trials are still warranted to improve the treatment results of PTCL patients presenting with advanced stages and high-risk features.

Ethics

Ethics Committee Approval: Memorial Hospital Ethics Committee (date: 09.12.2021/decision no: 27).

Informed Consent: All patients gave written informed consent at the time of hospital admission and before any diagnostic evaluation, invasive procedures, or chemotherapy in line with the standard policies of the participating centers.

Authorship Contributions

Concept: E.T., Ö.K., İ.S.; Design: E.T., Ö.K., İ.S.; Data Collection or Processing: E.T., Ö.K., İ.S.; Analysis or Interpretation: E.T., Ö.K., İ.S.; Writing: E.T., Ö.K., İ.S.; Final Approval: Ö.K., Ö.M., İ.S., F.D., C.B., G.Ç., F.V., M.Y., E.Ö., S.A., B.E., M.G., Y.B., B.P., R.Y., M.H.D., A.Ö., E.K., E.T.

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References

1. Vose J, Armitage J, Weisenburger D; International T-Cell Lymphoma Project. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 2008;26:4124-4130.
2. Savage KJ, Chhanabhai M, Gascoyne RD, Connors JM. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Ann Oncol 2004;15:1467-1475.
3. Mak V, Hamm J, Chhanabhai M, Shenkier T, Klasa R, Sehn LH, Villa D, Gascoyne RD, Connors JM, Savage KJ. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. J Clin Oncol 2013;31:1970-1976.
4. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, International Agency for Research on Cancer, 2017.
5. Coiffier B, Brousse N, Peuchmaur M, Berger F, Gisselbrecht C, Bryon PA, Diebold J. Peripheral T-cell lymphomas have a worse prognosis than B-cell lymphomas: a prospective study of 361 immunophenotyped patients treated with the LNH-84 regimen. Groupe d'Etude des Lymphomes Agressives (GELA). Ann Oncol 1990;1:45-50.
6. Foss FM, Zinzani PL, Vose JM, Gascoyne RD, Rosen ST, Tobinai K. Peripheral T-cell lymphoma. Blood 2011;117:6756-6767.
7. Adams SV, Newcomb PA, Shustov AR. Racial patterns of peripheral T cell lymphoma incidence and survival in the United States. J Clin Oncol 2016;34:963-971.
8. Ellin F, Landström J, Jerkeman M, Relander T. Real-world data on prognostic factors and treatment in peripheral T cell lymphomas: a study from the Swedish Lymphoma Registry. Blood 2014;124:1570-1577.
9. Pedersen MB, Hamilton-Dutoit SJ, Bendix K, Møller MB, Nørgaard P, Johansen P, Ralfkiaer E, Brown Pde N, Hansen PB, Jensen BA, Madsen J, Schöllkopf C, d'Amore F. Evaluation of clinical trial eligibility and prognostic indices in a population-based cohort of systemic peripheral T cell lymphomas from the Danish Lymphoma Registry. Hematol Oncol 2015;33:120-128.
10. Janikova A, Chloupkova R, Campr V, Klener P, Hamouzova J, Belada D, Prochazka V, Pytlik R, Pirnos J, Duras J, Mocikova H, Bortlicek Z, Kopalova N, Mayer J, Trneny M. First-line therapy for T cell lymphomas: a retrospective population-based analysis of 906 T cell lymphoma patients. Ann Hematol 2019;98:1961-1972.
11. Iqbal J, Wright G, Wang C, Rosenwald A, Gascoyne RD, Weisenburger DD, Greiner TC, Smith L, Guo S, Wilcox RA, Teh BT, Lim ST, Tan SY, Rimsza LM, Jaffe ES, Campo E, Martinez A, Delabie J, Braziel RM, Cook JR, Tubbs RR, Ott G, Geissinger E, Gaulard P, Piccaluga PP, Pileri SA, Au WY, Nakamura S, Seto M, Berger F, de Leval L, Connors JM, Armitage J, Vose J, Chan WC, Staudt LM; Lymphoma Leukemia Molecular Profiling Project and the International Peripheral T-cell Lymphoma Project. Gene expression signatures delineate and prognostic subgroups in peripheral T-cell lymphoma. Blood 2014;123:2915-2923.
12. Parrilla Castellar ER, Jaffe ES, Said JW, Swerdlow SH, Ketterling RP, Knudson RA, Sidhu JS, Hsi ED, Karikehalli S, Jiang L, Vasmatzis G, Gibson SE, Ondrejka S, Nicolae A, Grogg KL, Allmer C, Ristow KM, Wilson WH, Macon WR, Law ME, Cerhan JR, Habermann TM, Ansell SM, Dogan A, Maurer MJ, Feldman AL. ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. Blood 2014;124:1473-1480.
13. Pedersen MB, Hamilton-Dutoit SJ, Bendix K, Ketterling RP, Bedroske PP, Luoma IM, Sattler CA, Boddicker RL, Bennani NN, Nørgaard P, Møller MB, Steiniche T, d'Amore F, Feldman AL. *DUSP22* and *TP63* rearrangements predict outcome of ALK-negative anaplastic large cell lymphoma: a Danish cohort study. Blood 2017;130:554-557.
14. Siaghani PJ, Song JY. Updates of peripheral T cell lymphomas based on the 2017 WHO classification. Curr Hematol Malig Rep 2018;13:25-36.
15. Weisenburger DD, Savage KJ, Harris NL, Gascoyne RD, Jaffe ES, MacLennan KA, Rüdiger T, Pileri S, Nakamura S, Nathwani B, Campo E, Berger F, Coiffier B, Kim WS, Holte H, Federico M, Au WY, Tobinai K, Armitage JO, Vose JM; International Peripheral T-cell Lymphoma Project. Peripheral T

cell lymphoma, not otherwise specified: a report of 340 cases from the International Peripheral T cell Lymphoma Project. Blood 2011;117:3402-3408.

16. Abramson JS, Feldman T, Kroll-Desrosiers AR, Muffly LS, Winer E, Flowers CR, Lansigan F, Nabhan C, Nastoupil LJ, Nath R, Goy A, Castillo JJ, Jagadeesh D, Woda B, Rosen ST, Smith SM, Evens AM. Peripheral T cell lymphoma in a large US multicenter cohort: prognostication in the modern era including impact of frontline therapy. Ann Oncol 2014;25:2211-2217.
17. Schmitz N, Trümper L, Ziepert M, Nickelsen M, Ho AD, Metzner B, Peter N, Loeffler M, Rosenwald A, Pfreundschuh M. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood 2010;116:3418-3425.
18. Tse E, Kwong YL. Diagnosis and management of extranodal NK/T cell lymphoma nasal type. Expert Rev Hematol 2016;9:861-871.
19. Corradini P, Tarella C, Zallio F, Dodero A, Zanni M, Valagussa P, Gianni AM, Rambaldi A, Barbui T, Cortelazzo S. Long-term follow-up of patients with peripheral T-cell lymphomas treated up-front with high-dose chemotherapy followed by autologous stem cell transplantation. Leukemia 2006;20:1533-1538.
20. d'Amore F, Relander T, Lauritzsen GF, Jantunen E, Hagberg H, Anderson H, Holte H, Österborg A, Merup M, Brown P, Kuittinen O, Erlanson M, Østenstad B, Fagerli UM, Gadeberg OV, Sundström C, Delabie J, Ralfkiaer E, Vornanen M, Toldbod HE. Up-front autologous stem-cell transplantation in peripheral T cell lymphoma: NLG-T-01. J Clin Oncol 2012;30:3093-3099.
21. d'Amore F, Relander T, Lauritzsen G, Jantunen E, Hagberg H, Holte H, Österborg A, Brown PD, Kuittinen O, Erlanson M, Østenstad B, Fagerli U, Anderson H, Liestøl K, Toldbod H. Ten years median follow-up of the Nordic NLG-T-01 trial on CHOEP and upfront autologous transplantation in peripheral T cell lymphomas. Hematol Oncol 2015;33(Suppl 1):139 (abstract).
22. Kharfan-Dabaja MA, Kumar A, Ayala E, Hamadani M, Reimer P, Gisselbrecht C, d'Amore F, Jantunen E, Ishida T, Bazarbachi A, Foss F, Advani R, Fenske TS, Lazarus HM, Friedberg JW, Aljurf M, Sokol L, Tobinai K, Tse E, Burns LJ, Chavez JC, Reddy NM, Suzuki R, Ahmed S, Nademanee A, Mohty M, Gopal AK, Fanale MA, Pro B, Moskowitz AJ, Sureda A, Perales MA, Carpenter PA, Savani BN. Clinical practice recommendations on indication and timing of hematopoietic cell transplantation in mature T cell and NK/T cell lymphomas: an International Collaborative Effort on Behalf of the Guidelines Committee of the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant 2017;23:1826-1838.
23. Kanate AS, Majhail NS, Savani BN, Bredeson C, Champlin RE, Crawford S, Giralt SA, LeMaistre CF, Marks DI, Omel JL, Orchard PJ, Palmer J, Saber W, Veys PA, Carpenter PA, Hamadani M. Indications for hematopoietic cell transplantation and immune effector cell therapy: guidelines from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant 2020;26:1247-1256.
24. Rodríguez J, Caballero MD, Gutiérrez A, Marín J, Lahuerta JJ, Sureda A, Carreras E, León A, Arranz R, Fernández de Sevilla A, Zuazu J, García-Laraña J, Rifon J, Varela R, Gandarillas M, SanMiguel J, Conde E. High-dose chemotherapy and autologous stem cell transplantation in peripheral T-cell lymphoma: the GEL-TAMO experience. Ann Oncol 2003;14:1768-1775.
25. Maurer MJ, Ellin F, Srour L, Jerkeman M, Bennani NN, Connors JM, Slack GW, Smedby KE, Ansell SM, Link BK, Cerhan JR, Relander T, Savage KJ, Feldman AL. International assessment of event-free survival at 24 months and subsequent survival in peripheral T-cell lymphoma. J Clin Oncol 2017;35:4019-4026.