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ORIGINAL ARTICLE

First-line therapy for T cell lymphomas: a retrospective population-based analysis of 906 T cell lymphoma patients

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Abstract

Peripheral T cell lymphomas (PTLs) have a globally poor prognosis. The CHOP regimen shows insufficient efficacy; first-line consolidation with autologous stem cell transplantation (auto-SCT) is a promising strategy but has never been confirmed by randomized data. We analyzed retrospectively 906 patients diagnosed with PTL between 1999 and 2015. Chemotherapy was given to 862 patients, and 412 of them were < 60 years. In this subset, we compared induction with CHOP (n = 113) vs. *CHOEP* (n = 68) and tested auto-SCT (n = 79) vs. no SCT (n = 73) in the intent-to-treat analysis. The median age of the whole cohort at diagnosis was 60 years (range; 18–91); the median follow-up was 4.3 years (range; 0.1–17.8). A shorter overall survival (OS) was associated with the male gender, age ≥ 60 years, stage III/IV, performance status ≥ 2, bulky tumor ≥ 10 cm, and elevated LDH. CHOEP induction showed a better 5-year PFS (*25.0%* vs. *32.9%*; *p.001*), and 5-year OS (*65.6%* vs. *47.6%; p.008*) than CHOP. Auto-SCT compared to no SCT brought a 5-year OS of 49.2% vs. 59.5% (*p.187*). Auto-SCT did not influence the OS in low-risk or low-intermediate risk PTLs. The high-intermediate and high-risk IPIs displayed a worse 5-year OS in auto-SCT arm (17.7% vs.46.2%; p.049); however, 73.9% of the patients never received planned auto-SCT. Our population-based analysis showed the superiority of CHOEP over CHOP in first-line treatment. We confirm the 5-year OS of around 50% in PTLs undergoing auto-SCT. However, the intended auto-SCT could not be given in 73.9% of the high-risk PTLs.

Keywords T cell lymphoma · Auto-SCT · Etoposide · Prognosis

Introduction

Peripheral T cell lymphomas (PTCLs) are an uncommon and heterogeneous group of disorders that constitute 5–20% of all non-Hodgkin's lymphomas (NHLs) depending on the geographical part of the world and ethnic group in question [1–3]. PTCLs comprise several distinct entities with regard to biology and clinical behavior. Except for primarily cutaneous T cell lymphoma and some leukemic forms, PTCLs are usually aggressive malignancies with a relapsing nature and poor

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response to therapy and poor prognosis [4–6]. With the exception of anaplastic lymphoma kinase-positive (ALK+) anaplastic large cell lymphoma (ALCL) and extranodal natural killer/T cell lymphoma (ENKTL) by the introduction of regimens containing L-asparaginase, the treatment results in PTCLs are generally much worse than in aggressive B cell non-Hodgkin lymphomas (B-NHLs) [7, 8]. There are several causes for this situation: (1) PTCLs represent only a minority of all NHLs with significantly high heterogeneity; (2) the lack of potent new drugs due to the small population for potential enrollment into randomized clinical trials; (3) the diagnostics of PTCLs are traditionally among the most difficult in hematology. Under such conditions, when sufficient results from large randomized trials are not available, the data derived from a population-based registry with long-term follow-ups can help in the identification of a truly efficient treatment strategy, and, moreover, these results can also be highly relevant to real patients.

Unlike B-NHLs, therapies based on cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) do not appear to be efficient enough in PTCLs. The addition of etoposide to CHOP (CHOEP) seems to bring better results in younger PTCL patients [3, 4]. With the exception of ENKTL, the experience of irradiation as a consolidation of the primary chemotherapy of PTCLs has yielded inconsistent results [3, 9–11]. The up-front intensification of therapy (high-dose chemotherapy) does not give unequivocal results and is still a matter for debate. The prospective phase 2 study of untreated systemic PTCLs shows that dose-dense induction followed by auto-SCT (high-dose therapy with autologous stem cell transplantation) is well tolerated and can lead to high long-term survival in younger patients with PTCLs [12, 13]. Despite the fact that auto-SCT has not been tested in the frame of randomized trials in PTCLs, there is some evidence from retrospective observation that this approach can be successful in this indication [3].

In our work, we have sought to comprehensively analyze a large cohort of PTCL patients from the Central European population using the prospectively maintained Czech Lymphoma Study Group (CLSG) database to better understand the prognostic factors affecting overall survival (OS), focusing specifically on the addition of etoposide and the role of high-dose chemotherapy in patients under 60 years of age in a first-line setting.

Methods

Patients

An initial total of 975 patients with newly diagnosed T cell lymphoma were identified in the CLSG database between 1999 and 2015. Of these 975 patients, 10 patients with inconsistency in the pathological review and 59 patients with no follow-up information were excluded, resulting in a total of 906 PTCL patients included in this analysis. The CLSG is a free association of university centers and authorized non-academic hematological and oncological centers in the Czech Republic. The CLSG database has at its disposal prospectively maintained data of newly-diagnosed lymphoma patients that cover approximately 70% of all adults (age ≥ 18 years) and non-Hodgkin lymphomas (NHLs), and 85% of all non-skin NHL patients in the Czech Republic (https://www.uzis.cz/cz/mkn/C81-C96.html). In the collaborating centers, trained data managers update the CLSG database, the Czech National Lymphoma Registry (NiHiL), in a continuous fashion. The set of required data is pre-defined for disease, staging, treatment, and follow-up, including selected laboratory parameters. Data for this analysis were selected directly by export from the CLSG database. The patients signed informed consent to data storage and collection before they were entered into the CLSG database. The diagnosis of PTCL was established locally, but there was a central retrospective pathological review (VC) of all local pathological reports according to the 2008 edition of the WHO classification of lymphoid neoplasms [14]. Inconclusive or incomplete reports were excluded. The CLSG database does not reliably cover skin T cell lymphomas, because the majority of these are managed at dermatology departments outside of participating CLSG institutions.

Patient stages were determined by the treating physician according to the Ann Arbor criteria, and, more recently, CLSG staging recommendations have also been used [15, 16]. The initial rigorous staging included, at minimum, thoracic and abdominal CT scans and unilateral bone marrow biopsies. No central review of the bone marrow biopsies was performed. PET or PET/CT has only been used in recent years. Complete blood counts and lactate dehydrogenase (LDH) tests were performed and recorded in the database. The patients' responses to treatment were assessed by the Cheson criteria (1999 or 2007) depending on the availability of PET scans [17, 18]. The treatment and outcomes, including response, time to progression, and survival were collected annually. The enrolled patients were followed until their death, withdrawal of consent, or inability to follow up.

Statistical analysis

Standard descriptive statistics were used to characterize the sample data set. A comparison of the categorical parameters was performed using the Fisher exact test. In the case of continuous variables, the Mann-Whitney test was used.

Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method, and all point estimates were accompanied by 95% confidence intervals. The OS was defined as the time from diagnosis to death from

any cause. The PFS was defined as the time from diagnosis to the date of the first documented progression/relapse or death. Patients who had not progressed/relapsed or died were censored as of the date of the last update. The comparison of OS and PFS between different subgroups (type of T cell lymphoma; CHOP vs. CHOEP; intention-to-treat auto-SCT vs. non-auto-SCT) was carried out by means of the logrank test.

Univariable and multivariable Cox proportional hazard models were used to evaluate the effect of all potential prognostic factors on the survival measures. The statistical significance of hazard ratios was assessed by means of the Wald test. As a level of statistical significance, $\alpha = 0.05$ was used.

First-line chemotherapy analysis

Patients under 60 years of age who were treated with CHOP or CHOEP only, who started treatment less than 3 months following their diagnosis, were qualified for first-line chemotherapy analysis. The assignment to the CHOP or CHOEP arm was determined according to the prevailing cycles of chemotherapy.

Autologous stem cell transplantation analysis

To analyze the effect of autologous stem cell transplantation, we selected patients under 60 years of age who were treated with CHOP or CHOEP in the first line and with no allogeneic consolidation in the first line. All the patients meeting the mentioned criteria were separated into two subgroups depending on whether auto-SCT was planned or not. Assignment to the intention-to-treat (ITT) auto-SCT group was made if there was any documented decision regarding this treatment at the time of therapy initiation. The ITT decision was not a standard part of the prospective data set in the CLSG database, and for this reason it was an addition required from the centers for the purpose of analysis.

Results

Population characteristics

At the time of the analysis (May 2017), 906 PTCL patients were suitable for an analysis of potential prognostic factors. The median age was 60 (range; 18–91 years) and males prevailed (59.4%). B-symptoms were present in (47.1%) patients, whereas bone marrow involvement was found in 19.2% cases, and other extranodal involvement in 66.6% patients. Elevated LDH was observed in 60.3% patients; clinical stages III or higher developed in 66.1% cases. Bulky disease (defined as mass ≥ 7.5 cm) was measured in 25.2% subjects; performance status of 0–2 (qualified by the ECOG scale) was exhibited by (87.6%) patients. All these characteristics were known in more than 93% of the patients, with the exception of bulky disease (78%). At the time of the analysis, 13,108 patients were registered in the CLSG database between 1999 and 2015 with any type of NHL (B cell chronic lymphocytic leukemia excluded), meaning that T cell lymphomas constituted approximately 7% of all newly-diagnosed systemic NHLs in the exclusively Caucasian population of the Czech Republic. In the last 5 years, the incidence of PTCLs registered in the CLSG database has remained stable, with around 70–80 new patients per year. This figure corresponds with the incidence of PTCLs at 0.7–1.1 cases per 100,000 people per year (74–116 new cases) in the Czech National Cancer Registry maintained by the Institute of Health Information and Statistics of the Czech Republic (https://www.uzis.cz/cz/mkn/C81-C96.html).

The most frequent T cell lymphoma subtypes were peripheral T cell lymphoma not otherwise specified (PTCL-NOS) with 328 (36.2%) patients, followed by anaplastic large cell lymphoma (ALCL) encompassing 270 (29.8%) cases, and angioimmunoblastic lymphoma (AITL) in 66 (7.3%) patients. Precise sub-classification was not possible in 65 (7.2%) patients; therefore, these cases were labeled as T cell non-Hodgkin's lymphoma (T-NHL) (Table 1).

Data about first-line therapy was available for 862/906 (95.1%) patients, and of these, 412/862 (47.8%) were younger than 60 years of age. Chemotherapy was administered in 363 of the 412 (88%) younger patients, while radiotherapy alone was used in 20 cases; the remaining 29 patients were treated with other types of local therapy (surgery, PUVA, etc.). The spectrum of first-line chemotherapy (patients under 60 years of age) was wide, with the majority of cases treated with CHOP ($n = 191$), CHOEP ($n = 78$), MegaCHOP/ESHAP ($n = 16$), PACEBO/SEQ protocol ($n = 22$), HyperCVAD ($n = 14$). The remaining 42 patients were treated with various different regimens, including CALGB protocol, COP, Promace/Cytabom, GMALL, Fludarabine-based regimens, CODOX-M/IVAC, etc.

Autologous stem cell transplantation in the first line was performed in 92/862 (10.7%) patients overall but in 70/412 (17%) patients under 60 years of age. Six patients underwent allogeneic stem cell transplantation. Additionally, only 41/906 (4.8%) patients were enrolled in clinical trials regardless of the time and phase of disease, but 31 (3.6%) were enrolled during first-line therapy.

The response was evaluated in 730 patients (according to Cheson 1999), with 543 (74.4%) patients achieving at least a partial response (CR and uCR of 58.4%) and 145 (19.9%) cases progressing [17]. According to the Cheson response criteria 2007, 551 PTCL patients were classified with an overall response rate (ORR) of 364 (66%) including 51.2% of CRs [18].

Table 1 Type of T cell lymphoma and overall and progression-free survival from diagnosis according to selected T cell lymphoma types

Type of T cell lymphoma	*N*	Overall survival		Progression-free survival	
		Median OS (95% CI)	Log-rank test *p* value*	Median PFS (95% CI)	Log-rank test *p* value*
PTCL-NOS	328	1.9 years (1.4–2.4)		1.0 years (0.9–1.2)	
ALCL	270	10.7 years (7.0–14.4)		4.4 years (1.6–7.2)	
ALCL ALK+	57	Not reached		Not reached	
ALCL ALK−	118	3.3 years (0.8–5.9)		1.6 years (0.3–2.8)	
ALCL ALKu	46	–		–	
C-ALCL	49	–		–	
AITL	66	4.3 years (1.4–7.2)		1.1 years (0.5–1.6)	
T-NHL	65	2.8 years (1.1–4.4)	< 0.001	1.0 years (0.6–1.4)	< 0.001
MF or SS	61	3.7 years (2.6–4.8)		2.7 years (1.6–3.8)	
NK/T-nasal	33	1.1 years (0.1–2.1)		0.7 years (0.4–1.0)	
EATL	30	2.7 years (0.7–4.8)		1.0 years (0.1–1.8)	
T-ALL/LBL	30	2.6 years (1.3–3.9)		1.7 years (0.5–2.9)	

PTCL-NOS peripheral T cell lymphoma not otherwise specified, *ALCL* anaplastic large-cell lymphoma, *AITL* angioimmunoblastic T cell lymphoma, *T-NHL* T-non-Hodgkin's lymphoma, *MF/SS* mycosis fungoides/Sézary syndrome, *EATL* enteropathy-associated T cell lymphoma, *T-ALL/LBL* T-acute lymphoblastic leukemia/lymphoblastic lymphoma

*For comparison of OS and PFS, ALCL were used regardless of the type

Prognostic factor analysis

The median follow-up for surviving patients was 4.3 years (range, 0.1–17.8 years). The global median OS and PFS of the whole T cell lymphoma cohort was 3.4 years (2.5–4.4; CI 95%) and 1.4 years (1.1–1.8; CI 95%), respectively. The best prognosis was showed by ALCLs (median OS 10.7 years; median PFS 4.4 years), followed by AITL (median OS and PFS 4.3 and 1.1 years, respectively). ALK+ ALCL compared to ALK− ALCL showed a better OS (median not reached vs. 3.3 years). An overview and comparison of selected T cell lymphomas are shown in Table 1, and the survival curves are depicted in Fig. 1.

The multivariable analysis of potential prognostic factors in T cell lymphoma patients ($n = 906$) identified the male gender, ages 60 and older, advanced stage (III–IV), performance status (PS 0/1, PS 0/≥ 2), bulky disease (≥ 10 cm) and LDH level (> upper limit of norm) as factors associated with worse overall survival (Table 2). The prognostic factors associated with shorter PFS remained ages under 60, stages III/IV of the disease, performance status (PS 0/≥ 2), and elevated LDH (Table 2). International Prognostic Index (IPI) and Prognostic Index for T cell lymphoma (PIT) scores (in the PTCL-NOS only) were calculated and confirmed the validity of both scoring systems for the stratification of patients [19, 20] (Fig. 2, Table 3).

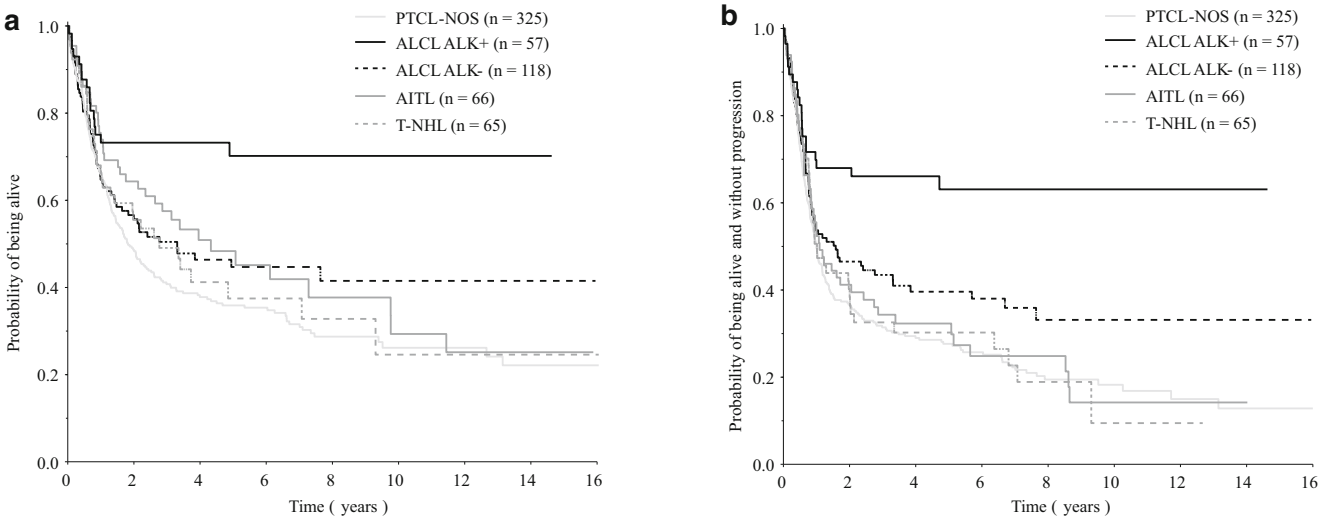


Fig. 1 Overall (**a**) and progression-free survival (**b**) from diagnosis according to selected T cell lymphoma types

Table 2 Results of the multivariable Cox analysis for overall and progression-free survival

Parameter	Tested category/reference category	*n*	Overall survival		Progression-free survival	
			HR (95% CI)	Wald test *p* value	HR (95% CI)	Wald test *p* value
Sex	Male/female	382/252	1.30 (1.03–1.63)	0.028	1.22 (0.99–1.50)	0.061
Age	≥ 60 years/< 60 years	313/321	1.81 (1.43–2.28)	< 0.001	1.33 (1.08–1.64)	0.007
B symptoms	Yes/no	309/325	1.19 (0.92–1.53)	0.189	1.12 (0.89–1.41)	0.336
Stage at diagnosis	Stage III-IV/I-II	424/210	1.59 (1.17–2.16)	0.003	1.51 (1.15–1.97)	0.003
Bone marrow involvement	Yes/no	111/523	1.17 (0.85–1.59)	0.336	1.14 (0.86–1.52)	0.374
Extranodal involvement	≥ 1/0	383/251	1.09 (0.83–1.42)	0.547	1.13 (0.89–1.44)	0.332
ECOG performance status	PS1/PS 0	225/219	1.54 (1.12–2.10)	0.008	1.31 (1.00–1.71)	0.054
	PS 2 or higher/PS 0	190/219	2.52 (1.82–3.49)	< 0.001	1.79 (1.34–2.39)	< 0.001
Bulky disease	≥ 10 cm/< 10 cm	101/533	1.53 (1.15–2.04)	0.003	1.30 (1.00–1.70)	0.055
DH	> ULN/≤ ULN	381/253	1.54 (1.20–1.99)	0.001	1.44 (1.15–1.81)	0.002
Type of T cell lymphoma[a]	ALCL/PTCL	213/245	0.70 (0.52–0.93)	0.015	0.71 (0.55–0.92)	0.009
	AITL/PTCL	56/245	0.60 (0.40–0.90)	0.013	0.87 (0.61–1.23)	0.418
	T-NHL/PTCL	40/245	1.14 (0.72–1.81)	0.567	1.12 (0.75–1.69)	0.578
	MF or SS/PTCL	16/245	1.05 (0.55–1.98)	0.890	0.94 (0.52–1.73)	0.851
	NK/T-nasal/PTCL	22/245	2.40 (1.36–4.22)	0.003	1.94 (1.12–3.35)	0.018
	EATL/PTCL	17/245	1.75 (0.88–3.45)	0.110	1.25 (0.68–2.32)	0.476
	T-ALL/LBL/PTCL	25/245	0.80 (0.44–1.46)	0.467	0.54 (0.31–0.96)	0.036

[a] Only types with at least 15 patients were included in analysis

First-line treatment analysis focused on the role of etoposide

For the analysis of induction treatment, 113 patients treated with CHOP and 68 patients treated with CHOEP were selected (patients with ALK+ ALCL were excluded). Both subgroups were similar, but there were statistically more patients with elevated LDH (72.1% vs. 52.3%; *p*.011) and B-symptoms (55.2% vs. 39.6%; *p*.046) in the CHOEP arm. Patients treated with the CHOEP combination had a significantly better PFS in 5 years compared to the cohort treated with CHOP (59.0% vs. 32.9%; *p*.001). This fact was also projected into better 5-year overall survival in the CHOEP subgroup (65.6% vs. 47.6%; *p*.008) (Table 4, Fig. 3). The results were also confirmed by the multivariable Cox proportional hazards model with the IPI score as a potential confounder to adjust the first-line chemotherapy result (etoposide) on different patients' prognoses (PFS and OS).

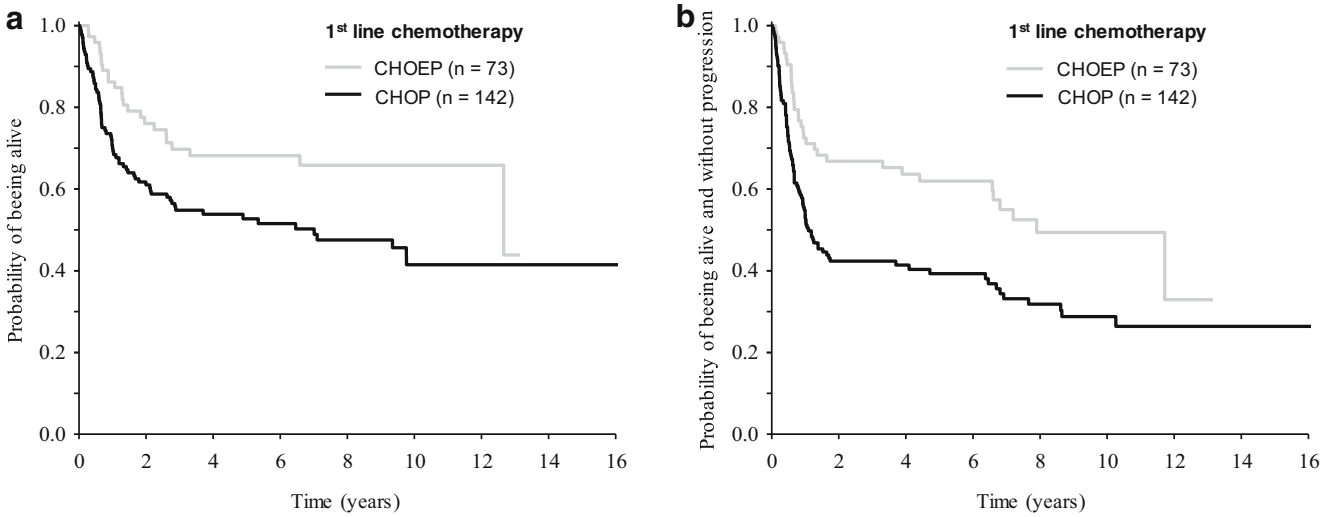


Fig. 2 Overall survival from diagnosis according to IPI (**a**) and PIT (**b**) score

Table 3 Overall survival from diagnosis according to IPI and PIT score

Characteristics		*n*	Overall survival		
			Median OS (95% CI)	5-year OS (%; 95% CI)	Log-rank test *p* value
IPI score	Low risk	273	not reached	72.1 (66.2–78.0)	< 0.001
	Low-intermediate risk	190	3.9 years (2.0–5.8)	47.3 (39.4–55.2)	
	High-intermediate risk	199	1.8 years (1.0–2.7)	38.4 (31.1–45.7)	
	High risk	183	0.7 years (0.5–1.0)	10.1 (4.5–15.8)	
PIT score[a]	Low risk	28	not reached	65.0 (46.2–83.7)	< 0.001
	Low-intermediate risk	88	6.6 years (1.9–11.2)	53.9 (42.3–65.5)	
	High-intermediate risk	100	1.7 years (1.2–2.2)	33.6 (23.7–43.4)	
	High risk	89	0.7 years (0.4–1.1)	10.4 (3.2–17.5)	

[a] Computed only for PTCL-NOS patients

Analysis of autologous stem cell transplantation in front-line therapy

To analyze the efficacy of consolidation with high-dose chemotherapy and autologous stem cell transplantation, we selected younger patients (< 60 years of age) treated with CHOP or CHOEP induction. Patients with ALK+ ALCL were excluded because of their excellent response to chemotherapy only. These criteria were met in 181 patients; 73 were planned and 79 were not initially planned for auto-SCT. The remaining 29 patients had no clear decision about auto-SCT in their initial plan.

We observed no significant difference in the 5-year OS among ITT non-SCT vs. auto-SCT and vs. patients without a clear auto-SCT decision as 59.5% (48.5–70.6%) vs. 49.2% (37.2–61.1%) and 53.1% (34.4–71.8%), respectively. The corresponding 5-year PFS for the above groups was 46.1% (35.0–57.3%) vs. 41.0% (29.5–52.5%) and 39.4% (21.3–57.6%; Table 5, Fig. 4). In the ITT auto-SCT subgroup, there were more patients with B-symptoms (*p*.024), advanced diseases (stage III or IV; $p < .001$), bone marrow infiltration (*p*.011), and a significantly lower number of low-risk patients (*p*.002). On the other hand, the ITT auto-SCT patients received intensive induction with CHOEP more frequently (47.9% vs. 32.9% vs. 24.1; *p*.049; Table 5). In the ITT auto-SCT group, however, there were 36 (49.3%) patients, who never received this treatment: 25 died (21 patients within 1 year from the date of diagnosis, mainly due to lymphoma progression) and 11 patients were alive at the date of the last follow-up.

Because of strong disproportions between groups of ITT auto-SCT and ITT non-transplanted patients, we added a subanalysis adjusted to IPI subgroups. For 67 low-risk patients, the 5-year OS was not different (70.8% vs. 68.3%; CI 95%; *p*.522) between ITT auto-SCT (42.9% of them were never transplanted) and ITT non-transplanted patients. For the low-intermediate risk group ($n = 41$), there was a tendency toward a better OS in ITT auto-SCT patients (but 38.5% of cases were never transplanted) at 5 years (55.8% vs. 45.7%; CI 95%; *p*.176). In the cohort of 46 high-intermediate and high-risk patients, the ITT auto-SCT subset (23 patients) showed a substantially worse 5-year OS (17.7% vs. 46.2%; CI 95%; *p*.049), but 17 (73.9%) cases never received the planned auto-SCT.

Discussion

Our report concerns data about T cell lymphomas in the Czech Republic, the population of which is very homogenous from an ethnic point of view with exclusive representation of Caucasian (white, non-Hispanic) individuals. It is well known that the distribution, etiology, and course of PTCL subtypes are dependent on the geographical zone and ethnic group. The existing published retrospective data of T cell lymphomas comes from countries, where mixtures of different ethnic groups are present to greater or lesser extents [2, 21, 22].

Therefore, the results from the CLSG Registry showed a lower incidence of PTCLs, with about 7% only in proportion to all NHLs, and a slightly different T cell lymphoma subtype distribution. A similar PTCL incidence was published using data from the Swedish population registry, but less than the generally cited incidence (10–15%) [3, 14, 23]. Concerning the particular lymphoma subtype, the proportion of PTCL-NOS (35.9%) and ALCL (29.8%) is comparable to the Swedish and Danish data [3, 23], but much higher than the results of the set from the USA (26–30% of PTCL-NOS and 12–18% ALCL) [1, 2]. The incidence of NK/T nasal lymphoma in the CLSG registry (3.6%) was comparable to European and North America data [2–4, 22], but lower than the global incidence in the world population (10–12%), where 80% of NK/T nasal cases were Asian or Hispanic whites [2, 5, 22]. EATL represented 3.3% of all PTCLs, which is in accordance with the Danish and American results, but lower than the

Table 4 Baseline characteristics according to first-line chemotherapy

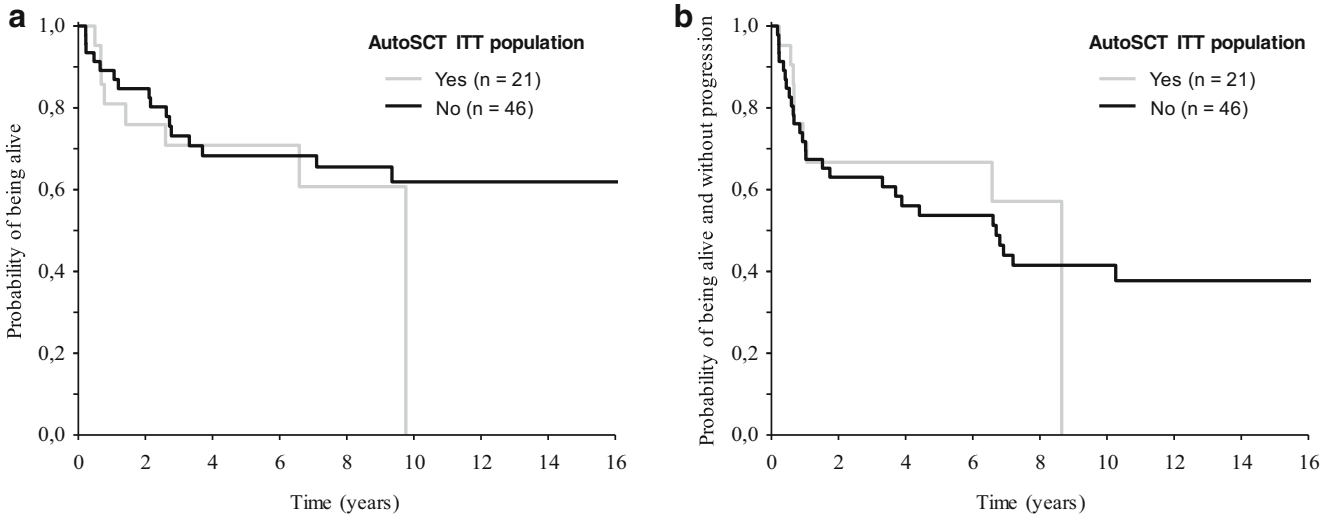
Characteristics[a], *n* (%)		Chemotherapy treatment		
		CHOEP (*n* = 68)	CHOP (*n* = 113)	*p*[b]
Sex	Male	44 (64.7)	77 (68.1)	0.745
	Female	24 (35.3)	36 (31.9)	
Age at diagnosis [years]	median (min-max)	51 (19–59)	49 (21–59)	0.763
B symptoms	Yes	37 (55.2)	44 (39.6)	0.046
	No	30 (44.8)	67 (60.4)	
Stage at diagnosis	I	12 (17.6)	10 (9.2)	0.265
	II	15 (22.1)	26 (23.9)	
	III	19 (27.9)	26 (23.9)	
	IV	22 (32.4)	47 (43.1)	
Bone marrow involvement	Yes	8 (11.9)	23 (20.4)	0.160
	No	59 (88.1)	90 (79.6)	
Extranodal involvement	0	29 (42.6)	42 (37.2)	0.530
	≥ 1	39 (57.4)	71 (62.8)	
ECOG PS	PS 0	33 (49.3)	45 (40.9)	0.595
	PS1	20 (29.9)	39 (35.5)	
	PS 2 or higher	14 (20.9)	26 (23.6)	
Bulky disease	≤ 10 cm	52 (91.2)	78 (85.7)	0.440
	> 10 cm	5 (8.8)	13 (14.3)	
LDH	≤ ULN	19 (27.9)	51 (47.7)	0.011
	> ULN	49 (72.1)	56 (52.3)	
IPI	Low risk	31 (46.3)	49 (47.1)	0.994
	Low-intermediate risk	20 (29.9)	29 (27.9)	
	High-intermediate risk	11 (16.4)	18 (17.3)	
	High risk	5 (7.5)	8 (7.7)	
Time from diagnosis to first-line treatment initiation (days)	median (mean)	17 days (24)	26 days (27)	0.260
First-line auto-SCT	Yes	20 (29.9)	19 (17.0)	0.061
	No	47 (70.1)	93 (83.0)	
Type of T cell lymphoma	PTCL-NOS	34 (50.0)	46 (41.4)	0.422
	ALCL ALK-	13 (19.1)	18 (16.2)	
	ALCL ALKu	4 (5.9)	12 (10.8)	
	C-ALCL	2 (2.9)	2 (1.8)	
	AITL	1 (1.5)	11 (9.9)	
	T-NHL	4 (5.9)	7 (6.3)	
	MF or SS	1 (1.5)	1 (0.9)	
	NK/T nasal	7 (10.3)	9 (8.1)	
	EATL	2 (2.9)	5 (4.5)	
5-years OS	% (95% CI)	65.6 (53.9–77.4)	47.6 (38.2–57.1)	0.008
5-years PFS	% (95% CI)	59.0 (47.0–71.0)	32.9 (24.0–41.7)	0.001

[a] All characteristics are known in more than 92% of patients, with exception of Bulky disease (81%)

[b] Fisher exact test, Mann-Whitney test or log-rank test

EATL incidence in Sweden [1, 3, 23]. In the Czech Republic, we observed a clearly lower incidence of AITL (7.3%), whereas the number of AITLs varies from 10.8% to 19% of the cases in other series [2, 3, 5, 23].

In our subset, there was a central review of pathological reports only, not a direct review of the biopsy samples. However, all the samples were directly reviewed by experienced hemopathologists in university centers. According to



* 9 patients (42.9 %) never received this treatment.

Fig. 3 Overall (**a**) and progression-free (**b**) survival from diagnosis according to first-line chemotherapy

the literature, possible diagnosis mistakes caused by this approach is assessed at between 3 and 17%, depending on the previous diagnostic process (provisional vs. formal diagnosis) and type of review [24, 25]. On the other hand, there is the considerable limitation of immunohistochemical and morphological T-lymphoproliferation diagnostics. Currently, it is supposed that about 37% of morphologically diagnosed PTCL-NOS cases will be reclassified into other subtypes by molecular signatures [26]. New insights into the pathology of PTCLs will help improve the differentiation of lymphoma subtypes [27].

Corresponding to the published data, we observed median OS and PFS of 3.4 and 1.4 years, respectively, for all PTCL patients [2, 5, 28]. The global ORR after first-line treatment was around 66.0–74%, according to selected response criteria (including 51–58% CRs), which is similar to the ORR in other published series. In our cohort, we confirmed the validity of PIT score for stratification of PTCL-NOS [20], but we were not able to validate the most recent prognostic index published by Federico et al. [29] because neutrophil counts are not part of the CLSG database data set and albumin levels were added 2 years ago, resulting in only 4% of patients with this parameter known.

We confirmed a high proportion of long-term survivors with ALK+ ALCL, where 8-year OS and PFS were 70.2% and 41.5%, respectively, while in patients with ALK− ALCLs, those measures were 44.7% and 33.1%. A similar analysis of 138 ALCL patients showed 8-year OS and PFS rates for patients with ALK+ as 82% and 72%, respectively, and for ALK− ALCL, 49% and 39% patients, respectively [7]. Data from the Swedish Lymphoma Registry concerning 219 ALCLs observed a 5-year OS for ALK+ and ALK− of 79% vs. 38%, and a 5-year PFS of 63% vs. 31%, respectively [3, 8]. In our cohort, AITL showed a 5-year OS of 48.3%, which seems to be slightly better than the published results with a 5-year OS of only about 30–35% [6].

Our results support the evidence that the addition of etoposide to the induction (CHOEP) probably brings a benefit to younger PTCL patients in terms of the prolongation of OS and PFS [3, 4, 30]. We must admit, however, that it is always difficult to know the effect of the therapy choice vs. the bias of the physician and subtle patient differences, which could influence treatment results.

In our cohort, the front-line auto-SCT was performed in 10.7% of patients (17% patients under 60 years) only. Regarding retrospective design, it was not possible to identify precise reasons for upfront auto-SCT selection, and there were no strict recommendation for this indication in the Czech Republic. Up to now, the official CLSG guidelines recommend considering auto-SCT in younger patients (up to 65 years) with PTCL-NOS, AITL, and ALCL ALK negative. The proportion of patients undergoing upfront auto-SCT varied between 10 and 20% in other published series [3, 23, 28]. Moreover, the most recent prospective analysis of 311 PTCL-NOS (2006–2015) observed only a 4% upfront auto-SCT [29].

The benefits of high-dose chemotherapy and auto-SCT have not been clear until now. Recent recommendations based on the published results of non-randomized studies support the use of first-line auto-SCT in patients with PTCL (with the exception of ALK+ ALCL) [12, 13, 31]. The large prospective phase 2 study on 160 untreated PTCLs showed that patients in remission after CHOEP induction and consolidated with auto-SCT have a 5-year OS of 51% [12, 13]. A similar 5-year OS of 51% (PFS was 44%) was reported by a German group in a large prospective study on 111 untreated PTCLs who underwent induction with CHOP and autologous stem cell consolidation [32]. Unfortunately, there was no

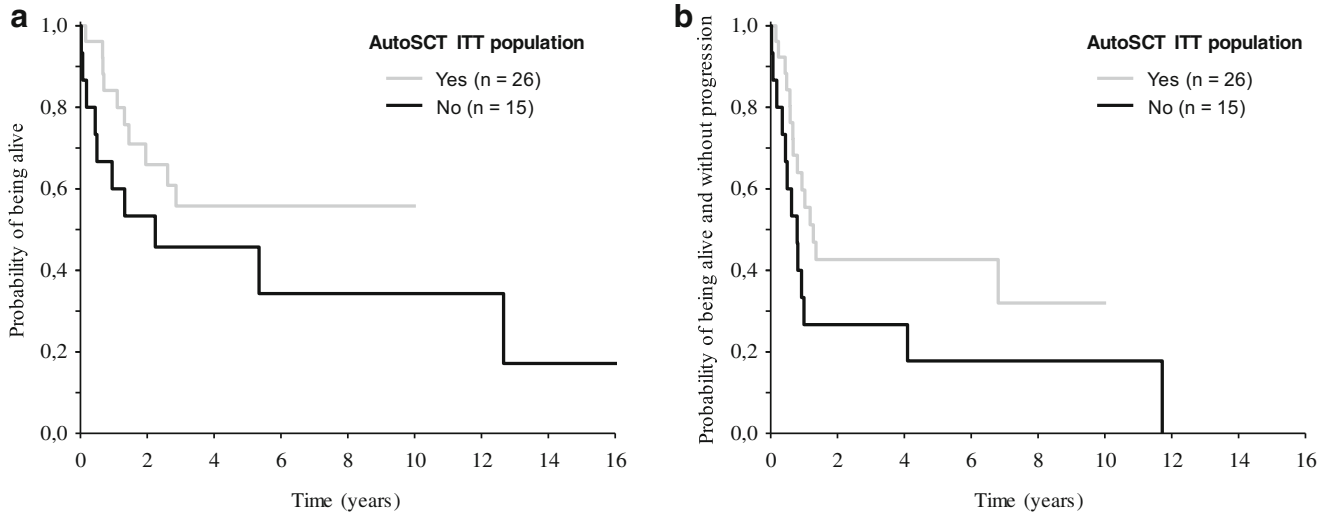
Table 5 Baseline characteristics according to plan for autologous stem cell transplantation

Characteristics[a], *n* (%)		Auto-SCT ITT population			p^b
		Yes (*n* = 73)	No (*n* = 79)	NA (*n* = 29)	
Sex	Male	53 (72.6)	49 (62.0)	19 (65.5)	0.374
	Female	20 (27.4)	30 (38.0)	10 (34.5)	
Age [years]	median (min-max)	51 (24–59)	49 (22–59)	46 (19–58)	0.308
B symptoms	Yes	42 (57.5)	27 (35.5)	12 (41.4)	0.024
	No	31 (42.5)	49 (64.5)	17 (58.6)	
Stage at diagnosis	I	2 (2.8)	15 (19.7)	5 (17.2)	< 0.001
	II	9 (12.5)	26 (34.2)	6 (20.7)	
	III	24 (33.3)	15 (19.7)	6 (20.7)	
	IV	37 (51.4)	20 (26.3)	12 (41.4)	
Bone marrow involvement	Yes	20 (27.4)	7 (9.0)	4 (13.8)	0.011
	No	53 (72.6)	71 (91.0)	25 (86.2)	
Extranodal involvement	0	28 (38.4)	35 (44.3)	8 (27.6)	0.290
	≥ 1	45 (61.6)	44 (55.7)	21 (72.4)	
ECOG PS	PS 0	27 (37.5)	40 (52.6)	11 (37.9)	0.256
	PS1	24 (33.3)	23 (30.3)	12 (41.4)	
	PS 2 or higher	21 (29.2)	13 (17.1)	6 (20.7)	
Bulky disease	≤ 10 cm	53 (82.8)	54 (88.5)	23 (100.0)	0.076
	> 10 cm	11 (17.2)	7 (11.5)	0 (0.0)	
LDH	≤ ULN	23 (31.9)	32 (42.1)	15 (55.6)	0.092
	> ULN	49 (68.1)	44 (57.9)	12 (44.4)	
IPI	Low risk	21 (30.0)	46 (62.2)	13 (48.1)	0.002
	Low-inter. risk	26 (37.1)	15 (20.3)	8 (29.6)	
	High-inter. risk	14 (20.0)	12 (16.2)	3 (11.1)	
	High risk	9 (12.9)	1 (1.4)	3 (11.1)	
1st line chemotherapy	CHOEP	35 (47.9)	26 (32.9)	7 (24.1)	0.049
	CHOP	38 (52.1)	53 (67.1)	22 (75.9)	
Type of T cell lymphoma	PTCL-NOS	39 (53.4)	32 (41.0)	9 (32.1)	0.089
	ALCL ALK-	13 (17.8)	15 (19.2)	3 (10.7)	
	ALCL ALKu	1 (1.4)	10 (12.8)	5 (17.9)	
	C-ALCL	1 (1.4)	3 (3.8)	0 (0.0)	
	AITL	7 (9.6)	3 (3.8)	2 (7.1)	
	T-NHL	6 (8.2)	2 (2.6)	3 (10.7)	
	MF or SS	1 (1.4)	1 (1.3)	0 (0.0)	
	NK/T nasal	3 (4.1)	8 (10.3)	5 (17.9)	
	EATL	2 (2.7)	4 (5.1)	1 (3.6)	
Allogeneic transplantation in 2nd or higher treatment line	Yes	7 (9.6)	9 (11.4)	1 (3.4)	0.645
	No	66 (90.4)	70 (88.6)	28 (96.6)	
5-years OS	% (95% CI)	49.2 (37.2–61.1)	59.5 (48.5–70.6)	53.1 (34.4–71.8)	0.187
5-years PFS	% (95% CI)	41.0 (29.5–52.5)	46.1 (35.0–57.3)	39.4 (21.3–57.6)	0.402

[a] All characteristics are known in more than 93% of patients, with exception of Bulky disease (77%)

[b] Fisher exact test, Mann-Whitney test or log-rank test

comparison with a non-transplanted group in both studies. The only comparison between transplanted and non-transplanted patients was made by the Swedish Lymphoma Registry's retrospective population-based analysis. The intention to treat the analysis of 252 patients revealed that auto-SCT vs. no transplantation was associated with a superior 5-year OS (48% vs. 26%; *p*.004) and 5-year PFS (41% vs. 20%; *p*.002) [3]. In this work, however, the subgroup of non-



* 10 patients (38.5 %) never received this treatment.

Fig. 4 Overall (**a**) and progression-free (**b**) survival from diagnosis according to plan for auto-SCT

transplanted patients was handicapped by a significantly higher median age (65 vs. 57 years; $p < .001$), by a higher proportion of patients treated by CHOP only (80% vs. 34%; $p < .001$), and a lower number of patients with IPI 0–1 (22% vs. 35%; $p.024$).

We can definitely confirm that upfront auto-SCT consolidation brings an approximate 50% survival probability at 5 years for PTCL patients under 60 years of age [3, 13], but we did not prove any benefits of front-line auto-SCT in PTCL after CHOEP/CHOP induction. Our conclusions are also supported by a recent study, where no significant benefit of intending first-line auto-SCT over non-transplant induction emerged in 117 patients with ALK− PTCL [33]. On the contrary, the prospective study enrolling 119 patients with nodal PTCL in first complete remission showed the survival benefit of auto-SCT especially for advanced stage disease and intermediate-to-high IPI patients [34]. It should be emphasized that our observations have some limitations due to the retrospective design and low number of analyzed subjects; and it cannot be excluded that only patients who were considered able to tolerate auto-SCT were entered. Moreover, there is a bias in our auto-SCT cohort with significantly more patients with increased LDH, B-symptoms, bone marrow involvement, advanced lymphoma, and higher IPI scores.

To diminish the bias, we performed additional auto-SCT analysis according to IPI subgroups. The patients with low IPI probably do not benefit from auto-SCT consolidation, whereas low-intermediate IPI patients display some trend (significance not reached) of having benefited from this procedure. High-intermediate and high-risk patients even seem to have a worse survival rate under auto-SCT compared to no SCT (0.9 vs. 2.8 years, respectively). However, this difference should be interpreted with the knowledge that 17 out of 23 (73.9%) ITT auto-SCT patients were never transplanted. The very low proportion of finally transplanted high-risk patients could not be statistically studied in greater depth due to the low numbers of subjects within the subgroups (according to IPI/ITT auto-SCT). It seems, however, that a higher proportion of patients who are non-responsive to induction therapy (progression, early relapse, stable disease) corresponded with higher IPI. Whereas the mean progression rate was 30% at the end of first-line (CHOP/CHOEP; < 60 years) for low IPI, there were 50% and 33% progressions in the high or high-intermediate IPI groups (data not shown). Our findings are in accordance with published data from prospective trials, where the transplantation rate varied from 41 to 74% and the progression rate before transplantation from 39 to 16% [12, 23, 32, 35, 36]. In these trials, there were no detailed analyses of never-transplanted patients according to IPI scores. These facts implicate that there is a very urgent need for efficient induction therapy for high-risk IPI patients with PTCL. CHOP or CHOEP seems to be insufficient for the majority of such patients.

Additionally, only 41 (4.8%) PTCL patients were enrolled into clinical trials regardless of the time and phase of the disease. By way of contrast, there were 2080 new follicular lymphomas diagnosed during the same period of 1999–2015, and 281 (13.5%) of them were enrolled in some kind of clinical trial according to the CLSG registry (data not shown). The low number of PTCL patients treated in the trials reflects the poor situation stemming from a lack of new, potentially effective, drugs.

Conclusion

In conclusion, our retrospective population-based analysis brings consistent results from one of the most robust

unselected T cell lymphoma cohorts. To date, there is practically no prospective randomized study comparing accessible treatment approaches. Thus, large retrospective population-based studies are the only source of evidence. We can confirm that the addition of etoposide to front-line therapy gives some benefit to younger PTCL patients. We can also confirm that first-line auto-SCT consolidation is able to provide good long-term results in terms of a 5-year OS of 50%. A substantial problem remains in the low efficacy of induction (CHOP or CHOEP) in high-risk IPI PTCL patients who cannot receive their planned auto-SCT consolidation, namely due to the progression of the lymphoma.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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