Non-anaplastic peripheral T cell lymphoma in children and adolescents—an international review of 143 cases

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ORIGINAL ARTICLE

Non-anaplastic peripheral T cell lymphoma in children and adolescents—an international review of 143 cases

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Abstract Peripheral T cell lymphomas (PTCL) are rare in children and adolescents, and data about outcome and treatment results are scarce. The present study is a joint, international, retrospective analysis of 143 reported cases of non-anaplastic PTCL in patients <19 years of age, with a focus on treatment and outcome features. One hundred forty-three patients, between 0.3 and 18.7 years old, diagnosed between 2000 and 2015 were included in the study. PTCL not otherwise specified was the largest subgroup, followed by extranodal NK/T cell lymphoma, hepatosplenic T cell lymphoma (HS TCL), and subcutaneous panniculitis-like T cell lymphoma (SP TCL). Probability of overall survival (pOS) at 5 years for the whole group was 0.56 ± 0.05, and probability of event-free survival was (pEFS) 0.45 ± 0.05. Patients with SP TCL had a good outcome with 5-year pOS of 0.78 ± 0.1 while patients with HS TCL were reported with 5-year pOS of only 0.13 ± 0.12.

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Twenty-five percent of the patients were reported to have a pre-existing condition, and this group had a dismal outcome with 5-year pOS of 0.29 ± 0.09. The distribution of non-anaplastic PTCL subtypes in pediatric and adolescent patients differs from what is reported in adult patients. Overall outcome depends on the subtype with some doing better than others. Pre-existing conditions are frequent and associated with poor outcomes. There is a clear need for subtype-based treatment recommendations for children and adolescents with PTCL.

Keywords Peripheral T cell lymphoma · Non-Hodgkin's lymphoma · Subtypes · Prognosis

Introduction

Non-anaplastic peripheral T cell lymphoma (PTCL) is a heterogeneous group of diseases that accounts for 0.9–1.8 % of all childhood non-Hodgkin's lymphoma (NHL) [1–5]. In the 2008 World Health Organization (WHO) classification, PTCL comprised 21 subtypes, including a leukemic/disseminated group, an extranodal group, a cutaneous lymphoma group, and a nodal group [6]. Epstein-Barr virus (EBV) is involved in the pathogenesis of many PTCL subtypes, and an alternative classification of EBV-positive T cell and NK cell lymphoproliferative diseases has been proposed [7].

The classification of PTCL has evolved over time with the introduction of newer diagnostic tools such as ALK-1 antibodies, anti-CD30 staining, and molecular-genetic methods. Thus, interpretation of published retrospective studies is difficult, since they often also included anaplastic large cell lymphomas (ALCL) into the group of PTCL. The most common subtypes of PTCL in adults are peripheral T cell lymphoma, not otherwise specified (PTCL NOS) occurring in 25 %, and angioimmunoblastic T cell lymphoma (AITL) occurring in 18.5 % of cases [4, 8]. Similarly, in children, PTCL NOS is the largest group while the diagnosis of AITL seems to be rare [1–3, 8, 9]).

Recent reviews on PTCL in pediatric and adolescent patients show that survival rates still are poor compared to other NHL sub-entities of this age group and that treatment results vary between PTCL subgroups [1–3, 9–11].

Systematic data on clinical characteristics, type of chemotherapy, and treatment outcome in larger cohorts of children and adolescents with PTCL are rare and all reported series relatively small. Thus, the two largest consortia in childhood NHL, the European Intergroup for Childhood NHL (EICNHL) and the international Berlin-Frankfurt-Münster (i-BFM) Study Group, designed a retrospective multinational study in which 143 patients with non-anaplastic PTCL were included. The aim of this retrospective study was to gather broader information on this rare entity of pediatric NHL, which could serve as a platform for the development of diagnostic and treatment guidelines for non-anaplastic PTCL in children and adolescents.

Patients and methods

Between March 2014 and December 2015, we performed an international retrospective survey of non-anaplastic PTCL in children and adolescents up to 19 years of age, diagnosed between 2000 and 2015. The analysis included only patients with a nationally reviewed histopathology from 16 EICNHL and/or i-BFM Study Group members.

The survey included questions on demographics and disease such as age, gender, stage, sites of involvement, as well as on treatment (type of chemotherapy, radiotherapy, stem cell transplantation) and outcome (date of relapse/progression, death, secondary malignancy, and last follow-up). Chemotherapy was classified by the national coordinator as either "lymphoblastic lymphoma/T cell type," "pulse-like B cell type," or "other" therapy. The diagnosis was based on morphological and immunophenotypic criteria according to the 2008 WHO classification [6]. Staging procedures are reported elsewhere. Notably, information about clinical presentation was too scarce to classify skin lymphomas correctly according to the staging systems for skin lymphomas developed by the International Society for Cutaneous Lymphomas and the European Organization for Research and Treatment of Cancer [12]. Instead, these patients were staged according to St Jude's staging system, where skin lesions only were classified as stage I.

All patients treated had informed consent from the patients, patients' parents, or legal guardians. Studies were conducted in accordance with the Declaration of Helsinki, and approval derived from the different ethic committees.

Statistical methods

Event-free survival (EFS) and overall survival (OS) rates were analyzed by the Kaplan–Meier method and compared by the log-rank test. Event-free survival was defined as the time from diagnosis to the first adverse event, defined as relapse or death, or date of last follow-up. Overall survival was defined as the time from diagnosis to death from any cause or date of last follow-up. Differences in proportions were assessed with the Chi-squared test, and P values less than 0.05 were considered significant. Results are reported as median values and range.

Results

Characteristics and outcome of all 143 patients with PTCL

By 1st January 2016, 168 patients with non-anaplastic PTCL were reported, but 25 patients (15 %) were excluded due to incomplete data. The remaining 143 patients (56 female and

87 male patients aged 0.3–18.7 years) are reported here. Twenty five of the patients were reported from Japan and Hong Kong, 13 from Canada, and the remaining 105 patients from European and Russian groups.

The number of patients in each of the histologic subgroups is shown in Table 1. Median age at diagnosis was at 11.1 years (range 0.3–18.7 years). Most patients were reported to have a stage III or IV (n = 58 and n = 39, respectively); stage was missing for one patient. Some subtypes mostly presented with stage I or II such as Extranodal NK/T cell lymphoma (EN NK/T CL) (n = 13/21) and mycosis fungoides (MF) (n = 5/7). In the group of stage III and IV patients, diseases such as hepatosplenic T cell lymphoma (HS TCL; n = 20/20), PTCL NOS (n = 46/60), and AITL (n = 4/4) were predominant. Eighty seven of the 143 patients (61 %) were alive at the date of last follow-up. Probability of OS (pOS) at 5 years for all patients was at 0.56 ± 0.05, and probability of EFS (pEFS) at 5 years was 0.45 ± 0.05. Relapse occurred in 39 patients (27 %) after a median time to relapse of 8 months (range 0–126 months). Twenty-five patients (17.5 %) were reported as refractory to primary chemotherapy.

One patient died from a car accident 66 months after treatment for subcutaneous panniculitis-like T cell lymphoma (SP TCL), and one patient with a Nijmegen breakage syndrome developed a second malignant neoplasm (acute myeloid leukemia) 43 months after treatment for a PTCL NOS. Twelve patients (8 %) died from toxicity during treatment or stem cell transplantation (SCT) with half of them having a pre-existing condition before the diagnosis of PTCL. Patients with advanced stage disease had a significantly worse outcome (n = 98) with a pOS at 5 years of 0.48 ± 0.06 as compared to patients with stage I and II (n = 26 and n = 19, respectively) having a pOS at 5 years of 0.69 ± 0.08 (p = 0.049; Fig. 1).

Overall survival varied according to histological subtype as shown in Fig. 2.

There was an equal distribution between T cell-based chemotherapy given in 49 patients (34 %) and B cell-based chemotherapy given in 55 cases (38 %). Twenty-seven patients (19 %) received miscellaneous treatment, 10 did not receive any treatment while in 2 patients, information about treatment strategy was not available (Table 1). There was no difference in outcome between the different treatment modalities; 36 of the patients treated with B cell type therapy (65 %) achieved complete remission (CR), 30 (61 %) treated with T cell type therapy, and 11 (41 %) treated with other type of treatments.

Twelve patients did not receive any chemotherapy. Two of these patients died from disease before start of treatment (PTCL NOS stage III and IV, respectively), one patient died in CR1 from an accident at 66 months from diagnosis of SP TCL stage II, and one patient was reported dead at 3 months from diagnosis without any further data (MF stage I). The remaining eight patients were all stage I or II (seven and one, respectively), diagnosed with EBV-related lymphoproliferative disease (EBV-pos LPD), MF, PTCL NOS, or SP TCL in the skin. These patients were treated with resection and/or wait and watch strategy, and were reported alive in CR1 at a median follow up of 32 months (range 0–99 months).

Forty-nine patients (34 %) underwent hematopoietic SCT; 25 in CR1, 15 in CR2, 6 in partial remission, and in 3 patients remission data is lacking. Twenty nine (59 %) of the transplanted patients survived, 18 after allogeneic SCT, 5 after autologous SCT, and 6 of the patients in whom type of transplant was not reported, resulting in a 5-year pOS of 0.58 ± 0.08 for this group. Data on SCT are summarized in Table 4.

Characteristics and outcome according to the different histological subtypes

The distribution of the histological subtypes and outcome are shown in Table 1 and details about clinical presentation in Table 2.

PTCL NOS

PTCL NOS were the most common subtype diagnosed in 60 patients (42 %). There was no significant difference in outcome between the 29 patients receiving B cell type and the 22 patients receiving T cell type of therapy. Three of the six patients treated with other type of therapy died and two of the three patients that did not receive any treatment. After a median follow-up of 32.5 months (range 0–229 months), pOS at 5 years for this group of PTCL was 0.56 ± 0.07, and pEFS at 5 years was 0.47 ± 0.07. Relapse occurred in 20 patients (33 %) after a median time to relapse of 8.5 months (range 1–126 months), 10 patients (17 %) were reported to have progressive disease, and 3 patients died from treatment-related toxicity. Sixteen patients (27 %) underwent SCT, 14 allogeneic, and 2 autologous. Six patients (37.5 %) were transplanted in CR1 and five of them are alive at the date of last follow-up. Nine patients were transplanted in CR2 (56 %) and five are alive. One patient transplanted in partial remission died.

Angioimmunoblastic T cell lymphoma

AITL was reported in four patients; two were EBV-negative. Median follow-up of the patients with AITL was 51.5 months (range 14–86 months).

Three of the patients (75 %) underwent SCT, one allogeneic and two autologous. All three patients were transplanted in CR1 and two of them survived.

Extranodal NK/T cell lymphoma

The second largest group was EN NK/TCL being reported in 21 patients (15 %).

Table 1 Distribution of the different histopathological subgroups as well as the treatment strategy and outcome of the 143 patients with PTCL

Histological subtype	Treatment type	Tot Nb	Res Dis	Relapse	SCT in CR1/PR	SCT in CR > 1	Alive	Dead
PTCL NOS (n = 60)	B cell type	29	2	9	1	6	17	12
	T cell type	22	2	8	2	3	15	7
	Other	6	3	2	3	0	3	3
	No treatment	3	0	0	0	0	1	2
EN NK/TCL (n = 21)	B cell type	8	0	4	0	1	4	4
	T cell type	9	0	4	0	1	5	4
	Other	4	0	3	1	0	3	1
	No treatment	0	–	–	–	–	–	–
HS TCL (n = 20)	B cell type	6	2	0	4	0	4	2
	T cell type	7	1	1	2	1	2	5
	Other	7	2	2	4	1	1	6
	No treatment	0	–	–	–	–	–	–
SP TCL (n = 20)	B cell type	9	0	2	2	1	8	1
	T cell type	4	0	1	1	0	4	0
	Other	4	1	0	1	0	2	2
	No treatment	3	0	0	0	0	2	1
MF (n = 7)	B cell type	0	–	–	–	–	–	–
	T cell type	1	0	0	1	0	1	0
	Other	1	0	0	0	0	1	0
	No treatment/nd	5	1	0	0	0	4	1
EBV-pos LPD (n = 6)	B cell type	1	0	0	0	0	1	0
	T cell type	2	0	0	1	0	2	0
	Other	2	0	0	2	0	2	0
	No treatment	1	0	0	0	0	1	0
AITL (n = 4)	B cell type	0	–	–	–	–	–	–
	T cell type	1	0	0	1	0	1	0
	Other	3	0	1	2	0	2	1
	No treatment	0	–	–	–	–	–	–
EBV-neg LPD (n = 3)	B cell type	1	0	0	1	0	0	1
	T cell type	2	1	0	1	0	0	2
	Other	0	–	–	–	–	–	–
	No treatment	0	–	–	–	–	–	–
PCGD TCL (n = 1)	B cell type	1	1	0	0	0	0	1
	T cell type	0	–	–	–	–	–	–
	Other	0	–	–	–	–	–	–
	No treatment	0	–	–	–	–	–	–
HV like EBV (n = 1)	B cell type	0	–	–	–	–	–	–
	T cell type	0	–	–	–	–	–	–
	Other	1	0	1	0	1	1	0
	No treatment	0	–	–	–	–	–	–

There was no clear difference in outcome between the eight patients receiving a B cell type of treatment (four dead) and the ten patients receiving a T cell type of treatment (four dead). Three patients received the SMILE-regimen described in adult patients, two of them relapsed after therapy and one remained in CR1. Eight patients received radiotherapy, five as part of the primary treatment, and three at relapse. Four of the five patients

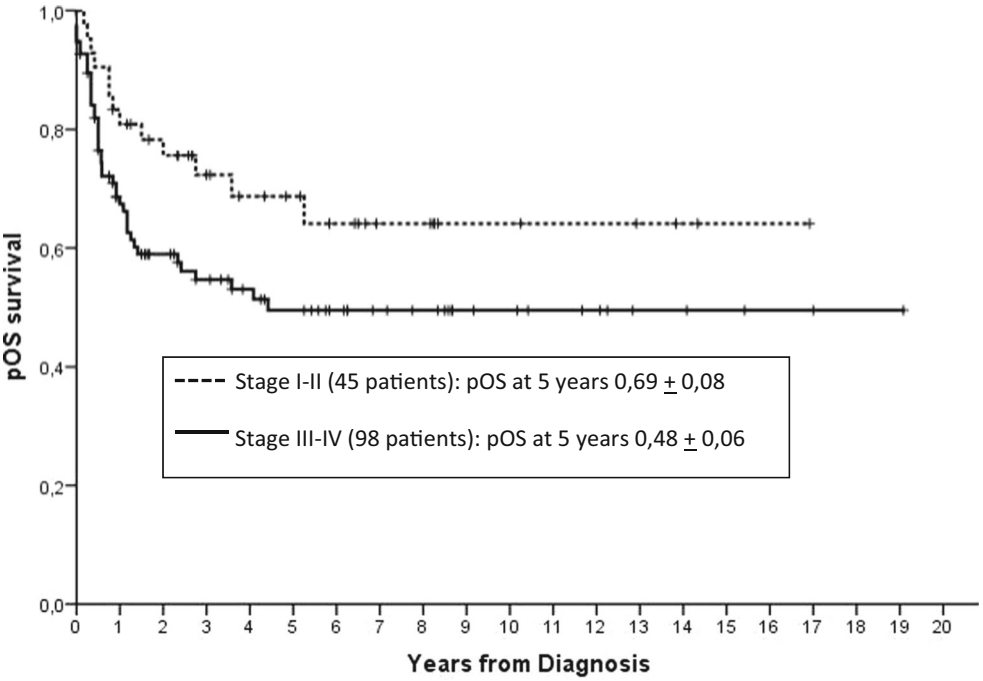

Fig. 1 Overall survival in the group of patients with stage I–II disease (45 patients) as compared to the patients with stage III–IV disease (98 patients); pOS at 5 years 0.69 ± 0.08 vs. 0.48 ± 0.06 ($p = 0.049$)

receiving radiotherapy as part of the initial treatment and one of the patients receiving irradiation at relapse were alive at the date of last follow-up. After a median follow-up of 31 months (range 0–204 months), pOS at 5 years for this group of PTCL was 0.57 ± 0.11, and pEFS at 5 years 0.34 ± 011. Relapse occurred in 11 patients (52 %) after a median time to relapse of 7 months (range 1–60 months); one patient (5 %) was reported to have progressive disease and two patients (9.5 %) died from treatment-related toxicity. Four patients (19 %) underwent SCT; one allogeneic, one autologous, and two in whom type of SCT was not available. One patient

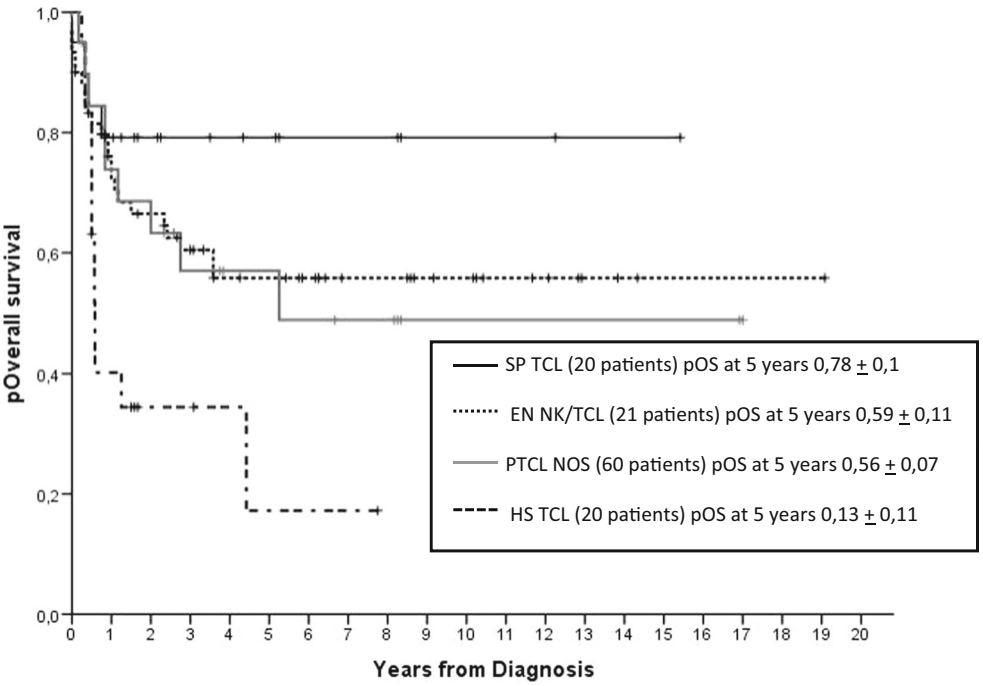

Fig. 2 Overall survival of patients with different histopathological subgroups, with SP TCL ($n = 20$) having a pOS at 5 years of 0.78 ± 0.1, followed by EN NK/TCL ($n = 21$) having a pOS at 5 years of 0.59 ± 0.11, PTCL NOS ($n = 60$) having a pOS at 5 years of 0.56 ± 0.07, and HS TCL ($n = 20$) having a pOS at 5 years of 0.13 ± 0.11

Table 2 Details about presentation in the 143 patients, according to the different histological subgroups

Histological subtype	Age at presentation	Sex	Stage at presentation		Sites at presentation							B-symp
	Median (min-max)	M/F	Stage I/II	Stage III/IV	LN	Liver/Spleen	Nasal	Skin/Subcut	BM	CNS	Effusions	
PTCL NOS (n = 60)	10.4 (1.1–18.6)	36/24	9/5	32/14	51	13/13	–	0	0	0	0	0
AITL (n = 4)	12.5 (7.8–16.3)	3/1	–	4/0	1	0/1	–	0	0	0	0	0
EN NK/TCL (n = 21)	12.8 (4.5–17.0)	12/9	6/7	6/2	6	3/3	15	0	0	0	0	0
HS TCL (n = 20)	14.7 (3.6–18.7)	12/8	–	3/17	6	18/17	–	0	0	0	0	0
SP TCL (n = 20)	8.0 (0.3–17.7)	12/8	5/5	10/0	3	4/4	–	0	0	0	0	0
MF (n = 7)	13.6 (7.2–16.6)	6/1	5/0	1/1	1	0/0	–	0	0	0	0	0
PCGD TCL (n = 1)	11.6	1/0	–	0/1	0	1/1	–	0	0	0	0	0
LPD (n = 9)	5.3 (1.7–12.6)	4/5	1/1[a]	2/4	6	1/1	–	0	0	0	0	0
HV like EBV (n = 1)	17.6	1/0	0/1	–	0	0/0	–	0	0	0	0	0

PTCL NOS peripheral T cell lymphoma not otherwise specified, *AITL* angioimmunoblastic T cell lymphoma, *EN NK/TCL* extranodal NK/T cell lymphoma, *HS TCL* hepatosplenic T cell lymphoma, *SP TCL* subcutaneaous panniculitis-like T cell lymphoma, *MF* mycosis fungoides, *PCGD TCL* primary cutaneous gamma-delta T cell lymphoma, *LPD* lymphoproliferative disease, *HV-like EBV* hydroa vacciniforme-like EBV-related T cell lymphoma, *M/F* male/female ratio, *LN* lymph node, *Liver/Spleen* liver and/or spleen involvement, *Skin-Subcut* skin lesions and/or subcutaneous nodules, *BM* bone marrow involvement, *CNS* CNS involvement, *Effusions* pleural or pericardial effusion and/or ascites, *B-symp* B-symptoms at diagnosis

[a] Stage missing in one patient

was transplanted in CR1 and was alive at the date of last follow-up. Two patients were transplanted in CR2, both alive, and for one patient remission status at SCT was not available.

Hepatosplenic T cell lymphoma

HS TCL was reported in 20 patients (14 %); 12 male and 8 female. Of the eight female patients, only one presented with stage III disease. There was a difference in outcome according to treatment strategy used as the six patients treated with B cell type treatment had the best outcome with a pOS of 0.62 ± 0.21 (two died) as compared to 0.21 ± 0.18 in the seven patients treated with a T cell type treatment (five died). None of the seven patient treated with other type of treatment survived (p = 0.003). There was no difference in outcome between male and female patients. Median follow-up time of patients with HS TCL was 6.8 months (range 0–93 months). Probability of OS at 5 years for the group was 0.13 ± 0.12. Relapse occurred during first month in three patients (15 %), nine patients (45 %) were reported to have progressive disease, and four patients (20 %) died from treatment-related toxicity. Twelve patients (60 %) underwent SCT, nine allogeneic and one autologous. Data about type of transplant was not available for two patients. Seven patients (58 %) were transplanted in CR1, and three of them were alive at the date of last follow-up. Two patients were transplanted in CR2 (17 %), and one of them is alive. Three patients (25 %) were transplanted in partial remission and one survived. Indeed, only seven patients (35 %) are alive at the date of last follow-up; five of these were transplanted (all allogeneic). Only one of the eight non-transplanted patients is alive. Two female patients had a pre-existing condition (primary immunodeficiency and previous transplantation) as compared to seven male patients (autoimmune disease/immunosuppressive therapy in four patients, previous malignancy, Nijmegen breakage syndrome, and previously transplantation in one patient each).

Subcutaneous panniculitis-like T cell lymphoma

SP TCL was diagnosed in 20 patients (14 %). None of the patients was reported with hemophagocytic lymphohistiocytosis (HLH).

Nine patients were treated with B cell type of treatment and one of them died. None of the four patients treated with T cell type of treatment died, and two of the four patients treated with other type of treatment died. Interestingly, only one of the three patients without treatment died. After a median follow-up time of 23 months (range 0–185 months), pOS at 5 years for this group of PTCL was 0.78 ± 0.1, and pEFS at 5 years was 0.74 ± 0.12. Relapse occurred in three patients (15 %) after a median time to relapse of 31 months (range 2–84 months), two patients (10 %) were reported to have progressive disease, and one patient (5 %) died from treatment-related toxicity. Five patients (25 %) underwent SCT, three allogeneic and two autologous. Three patients (50 %) were transplanted in CR1 and are all alive at the date of last follow-up. One patient transplanted in CR2 as well as one patient transplanted in partial remission died.

Mycosis fungoides

MF was diagnosed in seven patients (5 %). One was treated with a T cell type of treatment, one with individual protocol, and five patients did not receive any chemotherapy. Only one patient died after a period of wait and watch strategy. After a median follow-up of 14 months (range 0–67 months), pOS at 5 years for this group of PTCL was 0.83 ± 0.15, and pEFS at

5 years was 0.75 ± 0.22. No patient was reported with a relapse, but one patient (14 %) had progressive disease and one patient (14 %) died from treatment-related toxicity. Two patients (28 %) underwent SCT, one allogeneic and one where data about type of SCT was lacking. One patient transplanted in CR1 and one patient transplanted with partial remission both survived.

Primary cutaneous gamma-delta T cell lymphoma

One patient was diagnosed with a primary cutaneous gamma-delta T cell lymphoma (PCGD TCL) after presenting with skin infiltrations, effusions, testicular involvement, and secondary HLH. Details about this patient have been published elsewhere [1].

Lymphoproliferative disease

Nine patients (6 %) were diagnosed with lymphoproliferative disease (LPD). Three of the patients presented with EBV-negative LPD after heart transplantation. The other six patients presented with EBV-positive LPD; one with a T cell post-transplant lymphoproliferative disease (PTLD) after SCT, and the other five without previous transplantation reported. Two patients received B cell type of therapy, four T cell type, two other type of treatment, and one patient did not receive any treatment. After a median follow-up of 85.5 months (range 28–169 months), pOS at 5 years for this group of PTCL was 0.65 ± 0.16, and pEFS at 5 years was 0.65 ± 0.16 %. None of the patients suffered from relapse, but one patient (11 %) was reported to have progressive disease and two patients (22 %) died from treatment-related toxicity. All three patients with EBV-negative disease died, and the six patients with EBV-positive LPD survived. Four patients (44 %) underwent SCT; all four allogeneic transplants in CR1 and two of them are alive at the date of last follow-up.

Hydroa vacciniforme-like EBV-related T cell lymphoma

One patient was diagnosed with a Hydroa vacciniforme-like EBV-related T cell lymphoma, stage II, at 17.6 years of age after a long history of hydroa vacciniforme skin vesicles. He initially was treated with Rituximab alone, but suffered a relapse and underwent allogeneic SCT in CR2. This patient is reported to be alive and in remission after a follow-up of 83 months.

Pre-existing condition or malignancy

Details about type of pre-existing condition and histological subgroups are shown in Table 3. Thirty-six patients (25 % of all PTCL cases), 23 male and 13 female, with a median age at diagnosis of 9.0 years (range 1.1–18.7 years) were reported to have a pre-existing condition or malignancy before the diagnosis of PTCL. Five patients (14 %) were reported with stage I (n = 2) or II (n = 3), and 31 patients (86 %) with stage III (n = 15) or stage IV (n = 16) disease. Lymph node involvement was reported in 17 of the patients (47 %) and skin involvement in 6 (17 %). Bone marrow involvement was reported in 16 patients (44 %), 1 with a concomitant CNS involvement. B-symptoms were reported in nine patients (25 %) and effusions (ascites and pleural effusions) in seven patients (19 %).

Treatment was given with B cell type therapy in 18 patients (50 %), T cell type in 9 patients (25 %), and other type of therapy in 9 patients (25 %). Eight patients (22 %) developed PTCL after a previous transplantation with hematopoietic SCT for severe aplastic anemia and myelodysplastic syndrome in two, liver in one, kidney in two, and heart in three patients. Four patients were reported with a syndrome (trisomy 21 in two, CATCH 22 in one, and a non-specified syndrome in one) and one patient with a human papillomavirus infection. Two patients had a previous history of NHL and developed PTCL as second malignant neoplasm. After a median follow-up of 11 months (range 0–169 months), pOS at 5 years for this group of PTCL was 0.29 ± 0.09, and pEFS at 5 years was 0.11 ± 0.07 (Table 4). Relapse occurred in 10 patients (28 %) after a median time to relapse of 4 months (range 0–42 months); 12 patients (33 %) were reported to have progressive disease, and 6 patients (17 %) died from treatment-related toxicity. One patient died after cardiac rejection. Sixteen patients (44 %) underwent SCT, 14 allogeneic, and 2 autologous. Five patients (31 %) were transplanted in CR1 and two of them are alive at the date of last follow-up. Five patients were transplanted in CR2 (31 %) and four are alive. Three patients were transplanted in partial remission and one survived. Survival in this group of patients was inferior as compared to patients without a pre-existing disease (pOS at 5 years, 0.29 ± 0.09 vs. 0.66 ± 0.05; $p < 0.001$; Fig. 3).

Discussion

This report is the largest study of non-anaplastic PTCL in pediatric and adolescent patients published so far. Histological subtypes of pediatric PTCL differ slightly from what is described in adults, and outcome varies between the subgroups with a good prognosis for patients with SP TCL, intermediate outcome for patients with PTCL NOS, and a very poor prognosis for patients with HS TCL. In contrast to adults, pre-existing conditions are present in a large number of children with PTCL (25 %), and their outcome appears to be worse than in those without pre-existing condition.

As described in earlier reviews of pediatric patients and in adults, PTCL NOS comprised the largest group of patients in our analysis (42 %). Most patients had advanced disease at

Table 3 The distribution of histopathological subgroups and type of pre-existing disease or malignancy in the 36 patients with PTCL and pre-existing conditions

	Autoimmune/IS therapy	PID	PTCL as SMN	Nijmegen	Syndrome	Previous Tx	Hepatitis
EBV-pos LPD	0	0	0	0	0	1	0
EBV-neg LPD	0	0	0	0	0	3	0
EN NK/TCL	0	2	0	0	2	0	0
HS TCL	4	1	1	1	0	2	0
HV like EBV	0	1	0	0	0	0	0
PTCL NOS	2	3	1	6	1	2	0
SP TCL	0	1	0	0	1	0	1

EBV-pos LPD EBV-related lymphoproliferative disease, *EBV neg LPD* EBV-negative lymphoproliferative disease, *EN NK/TCL* extranodal NK/T cell lymphoma, *HS TCL* hepatosplenic T cell lymphoma, *HV like EBV* hydroa vacciniforme-like EBV-related T cell lymphoma, *PTCL NOS* peripheral T cell lymphoma not otherwise specified, *SP TCL* subcutaneous panniculitis-like T cell lymphoma, *Autoimmune/IS therapy* autoimmune disease and/or immune suppressive therapy, *PID* primary immune deficiency, *Nijmegen* Nijmegen breakage syndrome, *Syndrome* other known syndrome, *Previous Tx* previous organ or stem cell transplantation, *Hepatitis* hepatitis B virus infection

diagnosis. In order of frequency, PTCL NOS were followed by EN NK/T CL, HS TCL, and SP TCL in 13–15 % of the cases. This distribution of histological subgroups is similar to what has been reported in other reviews of pediatric cases [1–3, 9]. Unlike that observed in adult populations, the diagnosis of AITL was rare with only four cases in our cohort. No case of enteropathy-associated T cell lymphoma was described. In adults, angioimmunoblastic T cell lymphoma (AITL) and enteropathy-type TCL occur mostly in the elderly with a mean age of 65 and 61 years, respectively, as reported in the International Peripheral T Cell and Natural Killer/T Cell Lymphoma Study [8]; it is therefore not surprising that these subtypes are rare in children, whereas SP TCL and HS TCL, which occur in younger adults with a mean age of 33 and 34 years, are represented to a higher percentage in the age group below 18 years [8]. Cytotoxic T cell lymphomas or lymphoproliferation within the skin and subcutaneous tissues are divided in two different entities in the present 2008 WHO classification; SP TCL, restricted to cases with αβ-phenotype and primary cutaneous gamma-delta T cell lymphoma (PCGD-TCL) with γδ-phenotype. Patients with SP TCL had the best outcome in our series, with a pOS at 5 years of 0.78, and this is in accordance to earlier reports [13, 14]. Only one patient in our series was diagnosed with PCGD TCL, and that patient died from disease, in accordance to what is known from the literature [15].

HS TCL was described in 13 % of the pediatric cases; all of them high-stage. HS TCL derives from CD4- and CD8-negative γδ T cells and has an aggressive clinical course with a fatal outcome in most adult patients [16]. The dismal prognosis could be confirmed in our series with pOS at 5 years of only 0.13. In our pediatric series, 40 % of the reported patients

Table 4 Outcome of patients undergoing hematopoietic stem cell transplantation

		AITL (n = 4)	EBV-pos LPD (n = 6)	EBV-neg LPD (n = 3)	EN NK/TCL (n = 21)	HS TCL (n = 20)	HV-like EBV (n = 1)	MF (n = 7)	PCGD TCL (n = 1)	PTCL NOS (n = 60)	SP TCL (n = 20)
Dead	No SCT	0	0	1	9	7	0	1	1	18	2
	SCT in CR1	1	0	2	0	4	0	0	0	1	0
	SCT in CR2	0	0	0	0	1	0	0	0	4	1
	SCT in PR	0	0	0	0	1	0	0	0	1	1
	No data	0	0	0	0	0	0	0	0	0	0
Alive	No SCT	1	4	0	8	1	0	4	0	25	12
	SCT in CR1	2	2	0	1	3	0	1	0	5	4
	SCT in CR2	0	0	0	2	1	1	0	0	5	0
	SCT in PR	0	0	0	0	2	0	1	0	0	0
	No data	0	0	0	1	0	0	0	0	1	0

AITL angioimmunoblastic T cell lymphoma, *EBV-pos LPD* EBV-related lymphoproliferative disease, *EBV-neg LPD* EBV-negative lymphoproliferative disease, *EN NK/TCL* extranodal NK/T cell lymphoma, *HS TCL* hepatosplenic T cell lymphoma, *HV-like EBV* hydroa vacciniforme-like EBV-related T cell lymphoma, *MF* mycosis fungoides, *PCGD TCL* primary cutaneous gamma-delta T cell lymphoma, *PTCL NOS* peripheral T cell lymphoma not otherwise specified, *SP TCL* subcutaneous panniculitis-like T cell lymphoma, *SCT* stem cell transplantation, *SCT in PR* stem cell transplantation in partial remission, *No data* no data on remission status at transplantation

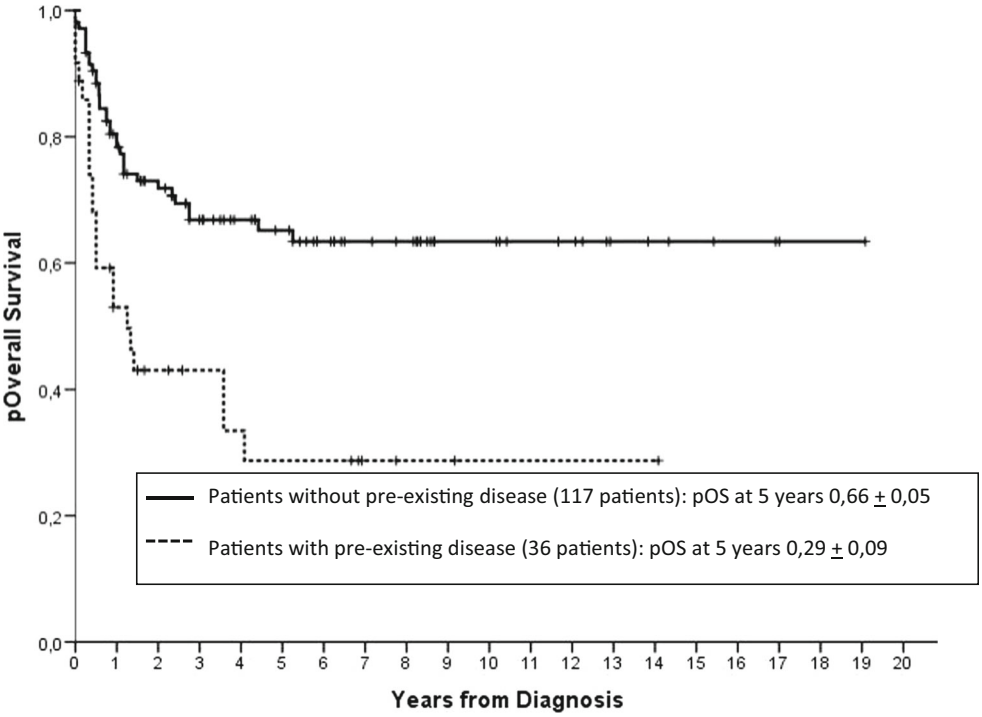

Fig. 3 Overall survival rate of the 36 patients with a pre-existing disease or malignancy (pOS at 5 years 0.29 ± 0.09) as compared to the other 117 patients (pOS at 5 years 0.66 ± 0.05; $p < 0.001$)

were females, which is higher than what is usually described. Female patients did not significantly differ in presentation and outcome as compared to male patients, but it is notable that none of the female patients had a history of autoimmune disease as seen in 25 % of the male patients. Earlier reports have suggested that αβ-phenotype of HS TCL is more common in female patients and our results would support that finding [17].

Extranodal NK/T CL, nasal type, is an aggressive disorder, often but not always associated with destructive midline lesions with necrosis, and associated with EBV. Whereas nasal involvement is the most common presentation, cases with gastrointestinal, cutaneous, testicular, bone, CNS, and even adrenal gland involvement have been described [7]. Fifteen percent of our pediatric cases were reported to have EN NK/T CL. In adult patients, the prevalence of NK/T CL differs according to geographical region, but this has not been confirmed in pediatric patients [18]. In our series, 33 % of the cases were reported from Japan or Hong Kong and the others from European groups. The outcome of these patients was relatively poor with pOS at 5 years of 0.57; indeed, a majority of the patients achieved complete remission, but relapse occurred in 50 % of the patients.

As reported in the adult population [19], most patients in our cohort of PTCL were reported to have stage III or IV disease and high-stage patients did have a worse outcome than patients with low-stage disease. This might be due to a difference in distribution of histological subtypes between low-stage patients and high-stage patients. Indeed, diseases such as MF and SP TCL were found more often in the low-stage group and more aggressive subtypes such as HS TCL and AITL exclusively in the high-stage group.

A surprising finding in our review was the high incidence of patients with a pre-existing condition such as Nijmegen breakage syndrome and primary immune deficiency, autoimmune diseases, and/or immune suppressive therapy as well as previous transplantation, which was found in overall 25 % of the patients. These patients did have an inferior outcome as compared to patients without pre-existing conditions, with relapse, or progressive disease reported in 60 % of the cases. The inferior prognosis of these patients is in accordance to what has been observed in other reviews of patients with pre-existing conditions (Attarbaschi A, personal communication). Indeed, earlier studies have pointed to the importance of underlying factors for lymphomagenesis, such as immune deficiency for young patients with Hodgkin's disease [20] and use of thiopurines with or without anti-TNFs, in patients with Crohn's disease [21]. We can only speculate about the mechanisms involved in our cohort of patients and an international effort would be necessary to establish treatment strategies to meet the specific needs of these patients.

In our review, the outcome of pediatric patients after treatment with conventional chemotherapy was better than what is generally reported for adults with pOS at 5 years for all patients of 0.55. Still, the outcome differed in different subgroups, suggesting a subtype-specific treatment approach being necessary in the future. We observed a better outcome for patients with HS TCL in the transplanted cohort, indicating a place to allogeneic SCT in the treatment of this disease. For other subtypes, our data is too scarce to clarify the place of SCT.

This retrospective study has several limitations; its retrospective nature may have led to under- or overestimation of

certain diagnosis and thereby influence the results of the study. All clinical details were not completely reported from the registers and descriptions of clinical presentation in the different subgroups might not be exhaustive. Also, data about treatment strategies are insufficient to make clear conclusions about optimal treatment strategies in the different subgroups and a more detailed review is clearly needed to clarify the role of SCT in the treatment of these patients.

In conclusion, our review has identified the largest group of non-anaplastic PTCL in pediatric and adolescent patients published so far. The distribution of histological subgroups and outcome differ slightly from what is described in the adult population, and a large proportion of patients did have a predisposing condition before the diagnosis of PTCL. This collaborative effort could be the first step to establish a multinational prospective registry for children and adolescents with PTCL to develop treatment recommendations for the different histological subtypes and for such a registry to be the platform for biological studies to improve our understanding of this heterogeneous group of patients.

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Authorship contributions DW, LB, AA, UK, and KM designed and planned the study. KM, UK, and AC were in charge of data pooling, data checking, and statistical analysis. All authors were principal or co-investigators in their study groups and institutions, coordinating national trials in their countries, providing study material, and recruiting patients. KM, UK, AA, and UA wrote the manuscript, and all authors read and approved the final version of the manuscript.

Compliance with ethical standards

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

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