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Primary post-transplant lymphoproliferative disorder of the central nervous system: characteristics, management and outcome in 25 pediatric patients

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Abstract

Primary central nervous system (CNS) post-transplant lymphoproliferative disorder (PTLD) of childhood is rare. Twenty-five patients were retrieved from nine European Intergroup for Childhood Non-Hodgkin's Lymphoma and/or international Berlin-Frankfurt-Münster Study Group members. Types of allografts included kidney (n=11), liver (n=4), heart (n=5), bowel (n=1), and hematopoietic stem cells (n=4). Eighteen were male, 16 ≥10 years-old, 21 had monomorphic disease and 24 solid intracranial tumor masses. Four-year event-free and overall survival rates were 50%±10% and 74%±9%, respectively. This report represents the largest pediatric series of CNS PTLD

reported to date, showing favorable survival odds following systemic and intrathecal chemotherapy and rituximab administration.

Introduction

Immunosuppression of children in the setting of solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HSCT) predisposes to post-transplant lymphoproliferative disorder (PTLD).[1] Epstein-Barr virus (EBV) is detected in ≥90% of cases and the most common sites of involvement are the lymph nodes and extra-cranial, extra-nodal sites.[2,3] A small proportion are confined to the central nervous system (CNS), either solely (primarily) or in addition to other sites. Given the rarity of primary pediatric CNS PTLD and a lack of prospective trials, reliable data are scarce, with most data having been extrapolated from case reports or small series, or combined with adults.[3-7] Thus, the European Intergroup for Childhood Non-Hodgkin's Lymphoma (EICNHL) and the international Berlin-Frankfurt-Münster (i-BFM) Group performed this retrospective analysis on primary pediatric CNS PTLD.

Methods

Data concerning clinical and laboratory features as well as outcome were retrospectively collected for children and adolescents ≤20 years-old with primary CNS PTLD diagnosed from 1997 to 2019 and reported by nine EICNHL and/or i-BFM members between July 2019 and March 2020. A diagnosis of PTLD was based on the World Health Organization classification valid at the time of diagnosis and primary CNS disease was defined by intracerebral/intraspinal mass(es) and/or cranial nerve palsies not caused by an extradural tumor and/or tumor cells in the cerebrospinal fluid (CSF) and/or involvement of the eye(s).[1,8] EBV-positivity was defined by the presence of EBV-RNA in the sample(s) analyzed by *in-situ* hybridization. Twenty-seven patients

with primary CNS PTLD were reported of whom two without a tumor biopsy performed were excluded from further analysis.

Data collection was approved by the respective ethics committees in case of patients enrolled into national trials/registries, while for non-trial/-registry patients, data collection was conducted with IRB approval.

Event-free survival (EFS) was calculated from the date of diagnosis to the date of a first event. Events were lack of complete response at the end of therapy (stable disease, partial remission), relapse/progression, secondary malignancy, or death. Overall survival (OS) was defined as the time from diagnosis to death from any cause or date of last follow-up. Survival curves were estimated according to the Kaplan-Meier method.

Results and discussion

The study population is shown in Table 1A-D. The male-to-female ratio was 18:7 and median age at PTLD diagnosis 11.78 years. Types of allografts included kidney (n=11; 44%), liver (n=4; 16%), heart (n=5; 20%), bowel (n=1; 4%), and hematopoietic stem cells (n=4; 16%). All but two patients (92%) received one or more immunosuppressive drugs at PTLD diagnosis. Median time between transplant and PTLD was 11 months. Twenty-one/25 (84%) patients had monomorphic PTLD. All but one monomorphic case (T-cell lymphoblastic lymphoma) had a diffuse large B-cell lymphoma (DLBCL; n=16) or mature B-cell non-Hodgkin's lymphoma (NHL) not otherwise specified (NOS; n=4). Polymorphic PTLD was diagnosed in the remaining 4/25 (16%) patients. The EBV-status of the tumor was available for 24/25 (96%) cases, of which 22 (92%) were positive. For 19/25 (76%) cases, the EBV-status of peripheral blood was available, with 12 (63%) being positive. Furthermore, the EBV-status of the CSF was available for 10/25 (40%) patients, of whom 4 (40%) were positive. Twenty-four/25 (96%) patients

had solid intracranial tumor masses, two (8%) additional intraspinal masses, and one (4%) leptomeningeal disease with cytomorphological CSF involvement only.

Immunosuppression was reduced (RIS) for 14/25 (58%) patients, while surgery (subtotal) was only attempted for 3/25 (12%) cases. Twenty-four/25 (96%) patients had systemic therapy. Therapies administered for >1 patient were recorded for 19/25 (76%) cases: chemotherapy only, n=3; rituximab only, n=3; chemotherapy + rituximab; n=6; chemotherapy + rituximab + steroids + radiotherapy, n=3; chemotherapy + rituximab + “others”, n=2; and rituximab + EBV-specific cytotoxic T-cells (CTLs), n=2. Chemotherapies included high-dose-methotrexate for two (8%), high-dose-cytarabine for four (16%), doxorubicin for three (12%) and cyclophosphamide for eight (32%) patients. Intrathecal therapies were given for 15/25 (60%) patients including triple therapies for 13 and rituximab for 10 cases.

Twelve/25 (48%) patients experienced no adverse event and are still alive being in first complete remission. Eight/25 (32%) patients failed to achieve a complete response including four with progression (PTLD-related death, n=2; death after multiple organ failure, n=1; alive, n=1), one with stable disease (alive) and three with partial remission (all alive) as reported by the local treating physicians. Of the remaining patients, 1/25 (4%) relapsed and died from PTLD, one suffered from a secondary malignancy of the kidney (renal cell carcinoma) as a first event following heart transplantation and died (cause unknown), and for 3/25 (12%) patients death occurred as a first event (therapy-associated, n=3). Notably, four (16%) patients lost their graft, all of them having received a kidney transplant (2 with a lack of complete response, 2 in first continuous complete remission). After a median follow-up of 4.59 years for surviving patients, 4-year EFS and OS were 50%±10% and 74%±9%, respectively (Figure 1).

Due to the low number of patients included in our analysis, prognostic factors were not assessed for outcome. Nevertheless, as PTLD after HSCT and SOT usually behaves differently, we compared the 4 HSCT and 21 SOT patients with each other, delineating that HSCT patients with primary CNS PTLD may have a worse response to therapy and EFS (Supplementary Table 1A-D). Another interesting observation was that 5 out of 8 deaths in our cohort occurred among the 10 patients diagnosed before and the remaining 3 deaths among the 15 patients diagnosed after 2010, suggesting an improvement in the management of primary pediatric CNS PTLD over time.

In a separate analysis of the 11 post-renal transplant patients (Supplementary Table 2A-D) we noted that all four patients with polymorphic PTLD within the whole cohort of 25 patients were among the kidney recipients, while the other seven post-renal transplant patients had DLBCL (n=4), T-cell lymphoblastic lymphoma (n=1) and mature B-cell NHL NOS (n=2). Therapies performed in >1 patient were reported for 8/11 (73%) patients: chemotherapy + rituximab, n=3; chemotherapy + rituximab + steroids + radiotherapy, n=3; and rituximab only, n=2. Six/11 (55%) are in first continuous complete remission, while 5/11 (45%) patients suffered from progression (n=2; both died), partial remission (n=2; both alive) or stable disease (n=1; alive) at the end of PTLD-therapy. With a median follow-up of 6.47 years for surviving patients, 5-year EFS and OS were 53%±15% and 89%±10%, respectively. Details regarding cardiac, liver, bowel and stem cell transplantation patients are shown in Supplementary Table 2A-D.

This report of 25 patients with primary CNS PTLD represents the largest series of this rare PTLD subtype in childhood and adolescence reported to date. Our analysis shows that primary CNS PTLD is associated with male gender, age ≥10 years, monomorphic disease such as EBV-positive mature B-cell NHL (mostly DLBCL), and solid intracerebral disease, and that almost 50% of our patients had undergone kidney

transplantation. Notably, half of the patients presented with early and half with late-onset disease and none had non-destructive PTLD. While EFS was only 50%±10%, OS was relatively good at 74%±9% for the whole cohort and even higher for the post-renal transplant patients at 89%±10%. Due to the retrospective and heterogenous nature of this dataset, the reasons for the favorable OS are difficult to discern, but are in contrast to the literature in which prognosis for primary pediatric CNS PTLD is generally reported as being poor.[4-7,9,10] Our 25 patients were treated with a variety of modalities at the discretion of the local treating institutions, including RIS, systemic and intrathecal chemotherapy and rituximab, rarely radiotherapy and EBV-specific CTLs in a few instances (three of four alive). The relatively low EFS rate might be due to the fact that the usage of doxorubicin, high-dose-methotrexate and high-dose-cytarabine, being cornerstones of classic pediatric NHL protocols/trials, were only rarely used up-front in this setting of PTLD occurring in a sanctuary site which can be penetrated by only a few cytotoxic drugs, used at high dosages.[11,12] Importantly, our group of 12 patients that survived in the absence of an event included all patients with doxorubicin-containing regimens, three of four patients having received high-dose-cytarabine, one of two having received high-dose-methotrexate, but only one of four with radiotherapy up-front and, in particular, only one of four HSCT patients.

Our study has several limitations including its retrospective nature with potential for reporting bias, the long-recruiting period including different managements of PTLD, and the inclusion of patients with different allografts. For sub-analyses, numbers were small. Nevertheless, given the rarity of this PTLD subtype, these multicentric data are likely to be the best available to assess disease characteristics and important factors for the consideration in the treatment and prognosis of primary pediatric CNS PTLD. This international collaboration let us conclude that primary pediatric CNS PTLD has quite favorable survival odds with a combination of systemic and intrathecal

chemotherapy and rituximab. Despite an increased risk for events, a step-wise process in treating CNS PTLD should still be followed, most likely including RIS and rituximab ± low-dose chemotherapy (including drugs such as cyclophosphamide, vinca alkaloids, corticosteroids and intrathecals) up-front and escalation with primary CNS lymphoma-derived chemotherapy containing high-dose-methotrexate and -cytarabine and, eventually, anthracyclines, after close monitoring of response to therapy.[12-15] Radiotherapy seems not to be indicated. An open question that remains to be answered is the most appropriate time point for intervention with EBV-specific CTLs, which, however, in case of non-responding disease, should be considered sooner rather than later.[16,17]

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Conflict-of-interest disclosure The authors declare no competing financial interests.

Authorship contributions

AA and MT designed and planned the study; AA, MT, BMK and SDT wrote the manuscript; AA, MT, RL, and AF were in charge of data pooling, data checking and statistical analysis; all other authors (SB, BB, AKSC, MC, AF, SH, JL, NM, VCM, and AU) as well as AA, MT, and BMK provided study materials and recruited patients. All authors read and approved the final version of the manuscript.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplementary Table 1. Clinical and therapeutic characteristics (A, B), biological features (C), and response and outcome (D) for the 25 primary CNS PTLD patients according to the type of allograft: hematopoietic stem cell *vs.* solid organ transplantation

Supplementary Table 2. Clinical and therapeutic characteristics (A, B), biological features (C), and response and outcome (D) for the 25 primary CNS PTLD patients according to the five types of allograft

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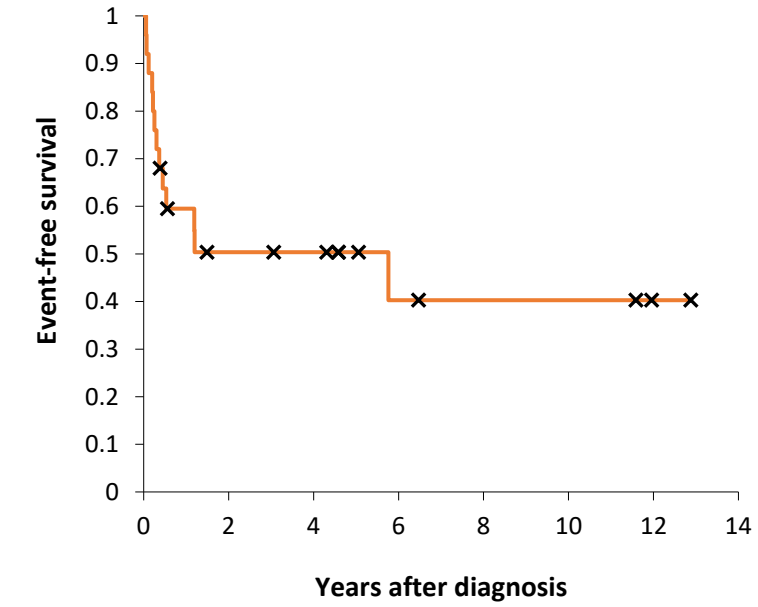
Figure 1. Four-year event-free survival (A) and overall survival (B) of the whole study cohort of 25 primary CNS PTLD patients

A

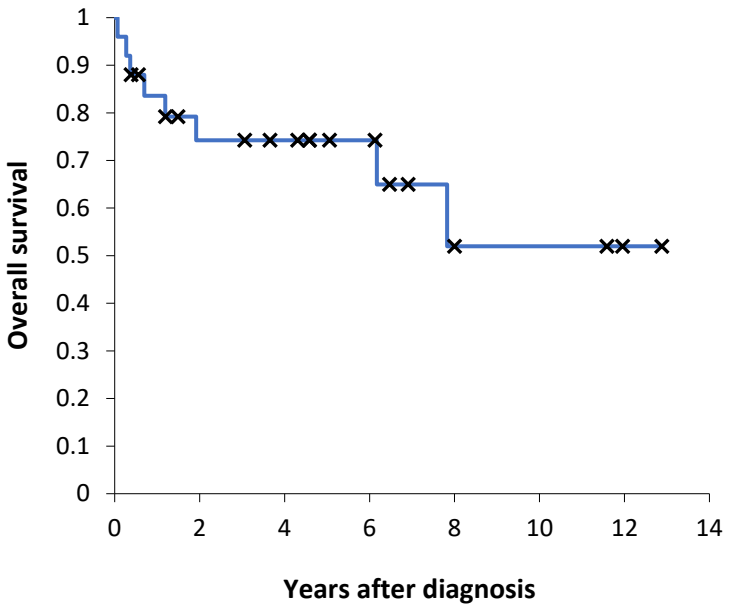


No. of patients at risk

25	11	10	5	4	4	1

4-year EFS: 50%±10% (25 patients; events: n=13)

B



No. of patients at risk

25	16	14	10	4	4	2

4-year OS: 74%±9% (25 patients; events: n=8)

Table 1. Clinical and therapeutic characteristics (A, B), biological features (C), and response and outcome (D) of the 25 primary CNS PTLD patients according to the histopathological subtype

A	Polymorphic PTLD	Monomorphic PTLD	∑
No. of patients	4	21	25
Gender			
female	0	7 (33%)	7 (28%)
male	4 (100%)	14 (67%)	18 (72%)
Organ Tx			
liver	0	4 (19%)	4 (16%)
heart	0	5 (24%)	5 (20%)
bowel	0	1 (5%)	1 (4%)
kidney	4 (100%)	7 (33%)	11 (44%)
HSCT	0	4 (19%)	4 (16%)
Time from Tx to PTLD			
median (years)	7.45	0.70	0.94
range (years)	5.99 - 10.89	0.30 - 9.40	0.30 - 10.89
<1 year	0	13 (62%)	13 (52%)
≥1 year	4 (100%)	8 (38%)	12 (48%)
Age at PTLD onset			
median (years)	13.65	10.98	11.78
range (years)	11.31 - 19.19	1.17 - 16.31	1.17 - 19.19
<10 years	0	9 (43%)	9 (36%)
≥10 years	4 (100%)	12 (57%)	16 (64%)
Immunsuppression at onset of PTLD			
tacrolimus	0	10 (48%)	10 (40%)
prednisolone	4 (100%)	12 (57%)	16 (64%)
mycophenolate mofetil	3 (75%)	11 (52%)	14 (56%)
other	1 (25%)	9 (43%)	10 (40%)
1 drug	0	4 (19%)	4 (16%)
≥2 drugs	4 (100%)	15 (71%)	19 (76%)
no drug	0	2 (10%)	2 (8%)

B	Polymorphic PTLD	Monomorphic PTLD	∑
No. of patients	4	21	25
B-Symptoms			
yes	0	6 (29%)	6 (24%)
no	3 (75%)	9 (43%)	12 (48%)
not available	1 (25%)	6 (29%)	7 (28%)
Cranial nerve palsies			
yes	1 (25%)	4 (19%)	5 (20%)
no	2 (50%)	8 (38%)	10 (40%)
not available	1 (25%)	9 (43%)	10 (40%)
Localization			
intracranial	4 (100%)	20 (95%)	24 (96%)
intraspinal only	0	0	0
leptomeningeal only	0	1 (5%)	1 (4%)
Initial therapy			
reduction of immunosuppression	3 (75%)	11 (52%)	14 (56%)
systemic therapy	3 (75%)	21 (100%)	24 (96%)
chemo only	0	3	3
rituximab only	1	2	3
chemo + rituximab	1	5	6
chemo + rituximab + RT + steroids	1	2	3
chemo + rituximab + steroids	0	1	1
chemo + rituximab + others	0	2	2
rituximab + RT + steroids	0	1	1
rituximab + CTLs	0	2	2
steroids + others	0	1	1
rituximab + steroids + CTLs	0	1	1
CTLs	0	1	1
no systemic therapy	1 (25%)	0	1 (4%)
Rituximab-containing therapy	3 (75%)	16 (76%)	19 (76%)
Chemotherapeutic drugs			
high-dose methotrexate	0	2 (10%)	2 (8%)
high-dose cytarabine	0	4 (19%)	4 (16%)
anthracyclines	0	3 (14%)	3 (12%)
alkylating agents	0	8 (38%)	8 (32%)
intrathecal therapies	1 (25%)	14 (67%)	15 (60%)
Radiotherapy			
yes	1 (25%)	3 (14%)	4 (16%)
no	3 (75%)	18 (86%)	21 (84%)

C	Polymorphic PTLD	Monomorphic PTLD	∑
No. of patients	4	21	25
Histopathological subtype			
DLBCL	/	16 (76%)	/
mature B-NHL NOS	/	4 (19%)	/
T-LBL	/	1 (5%)	/
EBER status of samples			
EBER-positive	3	19 (90%)	22 (88%)
EBER-negative	0	2 (10%)	2 (8%)
not available	1	0	1 (4%)
EBV-PCR results of PB			
positive	3	9 (43%)	12 (48%)
negative	1	6 (29%)	7 (28%)
not available	0	6 (29%)	6 (24%)
EBV-PCR results of CSF			
positive	0	4 (19%)	4 (16%)
negative	0	6 (29%)	6 (24%)
not available	4	11 (52%)	15 (60%)

D	Polymorphic PTLD	Monomorphic PTLD	∑
No. of patients	4	21	25
Response of initial disease			
complete response	2 (50%)	15 (71%)	17 (68%)
partial response	1 (25%)	2 (10%)	3 (12%)
stable disease	1 (25%)	0	1 (4%)
progressive disease	0	4 (19%)	4 (16%)
First event			
no event	2 (50%)	10 (48%)	12 (48%)
lack of complete response	2 (50%)	6 (29%)	8 (32%)
relapse	0	1 (5%)	1 (4%)
second malignancy	0	1 (5%)	1 (4%)
death	0	3 (14%)	3 (12%)
Overall outcome			
median FU of surviving pts. (years)	7.45	4.31	4.59
follow-up range (years)	4.59 - 11.96	0.39 - 12.88	0.39 - 12.88
alive in first CR	2 (50%)	10 (48%)	12 (48%)
overall alive	4 (100%)	13 (62%)	17 (68%)
death	0	8 (38%)	8 (32%)
PTLD-related	/	3	3
therapy of PTLD-related	/	4	4
cause of death unknown	/	1	1
4-year EFS	50%±25%	50%±11%	50%±10%
4-year OS	100%	69%±11%	74%±9%

Abbreviations: No., number; Tx, transplantation; HSCT, hematopoietic stem cell transplantation; PTLD, post-transplantation lymphoproliferative disease; chemo, chemotherapy; RT, radiotherapy; CTLs, cytotoxic T-lymphocytes; DLBCL, diffuse large B-cell lymphoma; NOS, not otherwise specified; T-LBL, T-cell lymphoblastic lymphoma; EBER, Epstein-Barr encoding region; EBV, Epstein-Barr virus; PCR, polymerase chain reaction; PB, peripheral blood; CSF, cerebrospinal fluid; FU, follow-up; CR, complete remission; EFS, event-free survival; OS, overall survival.

Supplementary Table 1. Clinical and therapeutic characteristics (A, B), biological features (C), and response and outcome (D) for the 25 primary CNS PTLD patients according to the type of allograft: hematopoietic stem cell *vs.* solid organ transplantation

A	**HSCT**	**SOT**	**∑**
No. of patients	4	21	25
Gender			
female	3 (75%)	4 (19%)	7 (28%)
male	1 (25%)	17 (81%)	18 (72%)
Organ Tx			
liver	/	4 (19%)	4 (16%)
heart	/	5 (24%)	5 (20%)
bowel	/	1 (5%)	1 (4%)
kidney	/	11 (52%)	11 (44%)
HSCT	/	0	4 (16%)
Time from Tx to PTLD			
median (years)	0.50	2.47	0.94
range (years)	0.35 - 0.62	0.30 - 10.89	0.30 - 10.89
<1 year	4 (100%)	9 (43%)	13 (52%)
≥1 year	0	12 (57%)	12 (48%)
Age at PTLD onset			
median (years)	11.38	12.22	11.78
range (years)	8.05 - 12.18	1.17 - 19.19	1.17 - 19.19
<10 years	1 (25%)	8 (38%)	9 (36%)
≥10 years	3 (75%)	13 (62%)	16 (64%)
Immunsuppression at onset of PTLD			
tacrolimus	0	10 (48%)	10 (40%)
prednisolone	1 (25%)	15 (71%)	16 (64%)
mycophenolate mofetil	2 (50%)	12 (57%)	14 (56%)
other	2 (50%)	8 (38%)	10 (40%)
1 drug	2 (50%)	2 (10%)	4 (16%)
≥2 drugs	1 (25%)	18 (86%)	19 (76%)
no drug	1 (25%)	1 (5%)	2 (8%)

B	HSCT	SOT	∑
No. of patients	4	21	25
B-Symptoms			
yes	1 (25%)	5 (24%)	6 (24%)
no	3 (75%)	9 (43%)	12 (48%)
not available	0	7 (33%)	7 (28%)
Cranial nerve palsies			
yes	1 (25%)	4 (19%)	5 (20%)
no	3 (75%)	7 (33%)	10 (40%)
not available	0	10 (48%)	10 (40%)
Localization			
intracranial	4 (100%)	20 (95%)	24 (96%)
intraspinal only	0	0	0
leptomeningeal only	0	1 (5%)	1 (4%)
Initial therapy			
reduction of immunosuppression	3 (75%)	11 (52%)	14 (56%)
systemic therapy	4 (100%)	20 (95%)	24 (96%)
chemo only	0	3	3
rituximab only	1	2	3
chemo + rituximab	1	5	6
chemo + rituximab + RT + steroids	0	3	3
chemo + rituximab + steroids	0	1	1
chemo + rituximab + others	1	1	2
rituximab + RT + steroids	0	1	1
rituximab + CTLs	1	1	2
steroids + others	0	1	1
rituximab + steroids + CTLs	0	1	1
CTLs	0	1	1
no systemic therapy	0	1 (5%)	1 (4%)
Rituximab-containing therapy	4 (100%)	15 (71%)	19 (76%)
Chemotherapeutic drugs			
high-dose methotrexate	1 (25%)	1 (5%)	2 (8%)
high-dose cytarabine	1 (25%)	3 (14%)	4 (16%)
anthracyclines	1 (25%)	2 (10%)	3 (12%)
alkylating agents	1 (25%)	7 (33%)	8 (32%)
intrathecal therapies	4 (100%)	11 (52%)	15 (60%)
Radiotherapy			
yes	0	4 (19%)	4 (16%)
no	4 (100%)	17 (81%)	21 (84%)

C	HSCT	SOT	∑
No. of patients	4	21	25
Histopathological subtype			
DLBCL	3 (75%)	13 (62%)	16 (64%)
mature B-NHL NOS	1 (25%)	3 (14%)	4 (16%)
T-LBL	0	1 (5%)	1 (4%)
polymorphic PTLD	0	4 (19%)	4 (16%)
EBER status of samples			
EBER-positive	4 (100%)	18 (86%)	22 (88%)
EBER-negative	0	2 (10%)	2 (8%)
not available	0	1 (5%)	1 (4%)
EBV-PCR results of PB			
positive	2 (50%)	10 (48%)	12 (48%)
negative	2 (50%)	5 (24%)	7 (28%)
not available	0	6 (29%)	6 (24%)
EBV-PCR results of CSF			
positive	2 (50%)	2 (10%)	4 (16%)
negative	2 (50%)	4 (19%)	6 (24%)
not available	0	15 (71%)	15 (60%)

D	HSCT	SOT	∑
No. of patients	4	21	25
Response of initial disease			
complete response	2 (50%)	15 (71%)	17 (68%)
partial response	1 (25%)	2 (10%)	3 (12%)
stable disease	0	1 (5%)	1 (4%)
progressive disease	1 (25%)	3 (14%)	4 (16%)
First event			
no event	1 (25%)	11 (52%)	12 (48%)
lack of complete response	2 (50%)	6 (29%)	8 (32%)
relapse	0	1 (5%)	1 (4%)
second malignancy	0	1 (5%)	1 (4%)
death	1 (25%)	2 (10%)	3 (12%)
Overall outcome			
median FU of surviving pts. (years)	3.65	4.82	4.59
follow-up range (years)	1.20 - 12.88	0.39 - 11.96	0.39 - 12.88
alive in first CR	1 (25%)	11 (52%)	12 (48%)
overall alive	3 (75%)	14 (67%)	17 (68%)
death	1 (25%)	7 (33%)	8 (32%)
PTLD-related	0	3	3
therapy of PTLD-related	1	3	4
cause of death unknown	0	1	1
4-year EFS	25%±22%	56%±11%	50%±10%
4-year OS	75%±22%	75%±9%	74%±9%

Abbreviations: No., number; Tx, transplantation; HSCT, hematopoietic stem cell transplantation; SOT, solid organ transplantation; PTLD, post-transplantation lymphoproliferative disease; chemo, chemotherapy; RT, radiotherapy; CTLs, cytotoxic T-lymphocytes; DLBCL, diffuse large B-cell lymphoma; NOS, not otherwise specified; T-LBL, T-cell lymphoblastic lymphoma; EBER, Epstein-Barr encoding region; EBV, Epstein-Barr virus; PCR, polymerase chain reaction; PB, peripheral blood; CSF, cerebrospinal fluid; FU, follow-up; CR, complete remission; EFS, event-free survival; OS, overall survival.