Risk factors, diagnosis, and management of posttransplant lymphoproliferative disorder: improving patient outcomes with a multidisciplinary treatment approach

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Abstract: Posttransplant lymphoproliferative disease (PTLD) is a major complication after solid organ transplantation and allogeneic hematopoietic stem cell transplantation. The spectrum of PTLD ranges from benign hyperplasia to malignant lymphoma, representing one of the most relevant malignancies in these patients. Most PTLDs are driven by latent Epstein–Barr virus infections. The backbone of treatment is reduction of immunosuppression. Further treatment depends on the type of PTLD and the type of transplantation. A multidisciplinary approach involving transplant team, hematologists, and other disciplines is crucial for the diagnosis and treatment of PTLD and for concurrent preservation of the transplant function. In this study, known pathomechanisms, risk factors, preemptive management, and especially emerging treatment algorithms in PTLD were reviewed.

Keywords: lymphoproliferative disease, Epstein-Barr virus, management, rituximab, preemptive therapy

Introduction

Posttransplant lymphoproliferative disease (PTLD) represents a spectrum of clinical and morphological heterogeneous lymphoid proliferations ranging from benign reactive hyperplasia to malignant lymphoma. PTLD develops in the setting of immunosuppression after solid organ transplantation (SOT) or allogeneic hematopoietic stem cell transplantation (HSCT).

It is one of the most common malignancy after both transplant settings, with an incidence ranging from 1% to 20%. It is usually associated with poor prognosis, with a 5-year overall survival rate of 20%.^{1,2} Its occurrence depends on the type of transplant received, the type of immunosuppression, its intensity and duration, and the age of the recipient.¹

Pathogenesis and classification

The majority of PTLD is Epstein–Barr virus (EBV) associated. Infection of B lymphocytes with EBV results in either viral replication, triggering cell death, or in latency. In the latency phase, the viral genome adopts an episomal configuration and expresses only a few proteins: the EBV nuclear antigens – EBNA-1, EBNA-2, EBNA-3A, EBNA-3B, EBNA-3C, and EBNA-LP; and the latent membrane proteins – LMP1, LMP2, and LMP3. LMP1 is considered as the main oncogenic protein, and it acts like CD40, a member of the tumor necrosis factor receptor superfamily.³ Through the activation

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of several downstream signaling pathways, LMP1 leads to the expression of anti-apoptotic proteins and cytokines (eg, BCL2 and interleukin 1), providing growth and differentiation signals to B cells independent of T-helper cell function.⁴

EBV-negative cases of PTLD are increasing in number.⁵ The etiology and pathogenesis of these lymphomas are not well understood. There are several hypotheses that explain the pathogenic mechanisms of EBV-negative PTLD: chronic immune stimulation by the graft, hit-and-run EBV infection, or other infectious agents, leading to the accumulation of genetic alterations and substituting the oncogenic effects of EBV.^{6–8} Comparison of EBV-positive and EBV-negative post-transplant (diffuse large B cell lymphoma) DLBCL showed that the latter contains more recurrent genomic lesions.⁹ Gene expression profiling studies have shown that EBV-negative PTLD are biologically distinct from their EBV-associated counterparts and more similar to EBV-negative de novo lymphomas in immunocompetent host.^{10,11}

Chromosomal and comparative genomic hybridization analyses show chromosomal aberrations in ~50% of PTLD cases.^{12–15} Mutations in *BCL6*, *MYC*, *PAX5*, *PIMI*, *RHOH* (4p13), or *NRAS* (1p13) are recurrent in PTLD. They may be related to somatic hypermutation occurring naturally in B cells.^{16,17} Inactivation of tumor suppressor genes (eg *DAPK1* and *MGMT*) has also been described.^{8,10,18}

The majority of PTLDs are of B-cell origin. T-cell or NK-cell PTLDs are rare, and EBV association can be identified only in ~30% of cases.¹⁹ In most B-cell PTLD, CD20 is expressed, although it has been shown that both polymorphic and monomorphic PTLDs have higher incidence of lack of CD20 as compared with de novo B-cell lymphoma.²⁰ PTLDs after SOT are of recipient origin, whereas PTLDs following HSCT are almost exclusively of donor origin and develop early after HSCT.^{21,22}

The 2008 WHO classification of lymphoid neoplasms recognizes four major histopathologic subtypes of PTLD: early hyperplastic lesions, polymorphic lesions (which may be polyclonal or monoclonal), monomorphic lesions (non-Hodgkin-type lymphomas), and classic Hodgkin-type lymphomas (Table 1).²³

Early lesions are often polyclonal and preserve the normal architecture of the affected tissues. They are further subdivided into infectious mononucleosis-like paracortical hyperplasia and plasmacytic hyperplasia. If untreated, a neoplastic clone can appear and transition to one of the more advanced subtypes of PTLD can occur.²³

In polymorphic PTLD, a mixture of small to large lymphocytes and immunoblasts can be seen. These cells

Table 1 WHO classification of PTLD

1. Early lesions
a. Reactive plasmacytic hyperplasia
b. Infectious mononucleosis-like lesions
2. Polymorphic PTLD
a. Polyclonal
b. Monoclonal
3. Monomorphic PTLD
a. B-cell neoplasms
Diffuse large B-cell lymphoma
Burkitt's lymphoma
Plasma cell myeloma
Plasmacytoma-like lesions
Others
b. T-cell neoplasms
Peripheral T-cell lymphoma not otherwise specified
Hepatosplenic T-cell lymphoma
Others
4. Classical Hodgkin's lymphoma-type and Hodgkin's lymphoma-like PTLD

Abbreviations: PTLD, posttransplant lymphoproliferative disease; WHO, World Health Organization.

include EBV-infected monoclonal B cells as well as reactive T lymphocytes. This lymphoplasmacytic proliferation is destructive but does not fulfill the strict criteria of malignant lymphoma.^{24–26}

In monomorphic PTLD, atypical lymphocytes resemble the conventional histopathologic types of B-cell malignancy (eg, diffuse large B-cell lymphoma, Burkitt lymphoma, anaplastic large cell lymphoma, and plasmacytoma). The vast majority of cases are associated with EBV infection/reactivation. These are more likely to occur late after transplantation, and they resample de novo B-cell lymphoma. Classical Hodgkin lymphoma-type PTLD is rare and makes the diagnosis of Hodgkin lymphoma-like polymorphic PTLD challenging because of a clear overlap.^{27,28}

Epidemiology and risk factors

After HSCT, the overall incidence of PTLD is rather low, ranging from 1% to 3%. The majority of PTLDs occurs early, within the first year of HSCT.^{29,30} PTLD rates are increased with the use of myeloablative conditioning regimen, in vivo or in vitro T-cell depletion with antithymocyte globulin (ATG) or monoclonal CD3 antibodies. The presence of GvHD and its treatment with ATG or other anti-T-cell antibodies also increases the risk, especially of late onset PTLD.^{30,31}

After SOT, PTLD is one of the most common malignancy, following nonmelanoma skin cancer.^{32–34} The cumulative incidence after 5 years ranges from 1% to 10%, with highest rates up to 33% in small bowel and multivisceral transplantation (Table 2).^{35,36} Major risk factors for developing PTLD

Table 2 Cumulative 1- and 5-year incidence of PTLD by transplanted organ as reported in the 2010 OPTN/SRTR Annual Report

Organ	Pediatric		Adult	
	After 1 year (%)	After 5 years (%)	After 1 year (%)	After 5 years (%)
Lung/heart–lung	4	16	1	1.5
Liver	2.1	4.7	0.25	1.1
Pancreas	N/A	N/A	2.3	2.3
Heart	1.6	5.7	0.3	0.7
Kidney	1.3	2.4	<0.2	0.6

Note: Data from Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR).³⁵

Abbreviations: N/A, not available; OPTN/SRTR, Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients; PTLD, posttransplant lymphoproliferative disease.

Table 3 Risk factors of PTLD

Risk factors
EBV seronegativity at the time of transplantation
Active primary EBV infection at the time of transplantation
Variants of <i>LMPI</i> gene sequence
T-cell depletion
Immunosuppressive drug regimen and intensity
Type of transplanted organ
Age (children and older patients)
CMV coinfection
Acute or chronic graft versus host disease
Second transplant
Prior splenectomy
HLA type
Extent of HLA mismatch

Abbreviations: CMV, cytomegalo virus; EBV, Epstein–Barr virus; HLA, human leukocyte antigen; *LMPI*, latent membrane protein 1; PTLD, posttransplant lymphoproliferative disease.

after SOT or HSCT are age at transplantation, pretransplant EBV mismatch, type of transplanted organ, T-cell depletion, and immunosuppression (Table 3).

Landgren et al³¹ conducted a large study of 21,686 HSCT patients and identified some major risk factors for developing PTLD after transplant. The most important risk factor was selective T-cell depletion and ATG use for prophylaxis or treatment of GvHD. Other significant risk factors were age >50 years, second HSCT, human leukocyte antigen (HLA) mismatch, and unrelated donor. The incidence of PTLD was low (0.2%) in the absence of risk factors, while an increased incidence (8.1%) was noticed in the subgroup of patients with more than three of the described risk factors.³¹

Regimen of immunosuppression and intensity play a very important role for the development of PTLD after HSCT and SOT. It appears that the most important factor is the degree of T-cell immunosuppression, as T-cell-specific immunity against EBV is impaired with increased impairment of T-cell function. Thus, ATG, anti-CD3 monoclonal antibodies, fludarabine, azathioprine, and other agents causing profound T-cell depletion significantly increase the risk of PTLD with a relative risk increasing up to 25% compared with the normal population.^{37–42} Conditioning with alemtuzumab also

increases the risk of PTLD, but the risk is much lower as seen in selective T-cell depletion.^{31,43,44}

In some retrospective analyses, tacrolimus compared with ciclosporin A in SOT patients increased the risk of PTLD, whereas other analyses did not show an increased risk with tacrolimus-based immunosuppression.^{37,40,43,45} Adding mycophenolate mofetil to a double immunosuppressive regimen was not associated with a further increase in the incidence of PTLD.^{46,47}

Immunosuppression with mammalian target of rapamycin inhibitors might have a positive effect on PTLD incidence. In experimental studies, mammalian target of rapamycin inhibitors like everolimus and sirolimus have been shown to inhibit transformed cells, such as EBV-transformed B cells.^{48,49} The sirolimus predrug temsirolimus represents a very effective treatment modality in mantle cell lymphoma supporting the B-cell inhibiting potential of these drugs.⁵⁰ However, the prevalence of PTLD under immunosuppression with mammalian target of rapamycin inhibitors needs to be defined in the settings of HSCT or SOT.

In SOT, HLA type may influence the ability of the immune system to present foreign epitopes. For example, HLA-A3 allele expression in recipient and/or donor was associated with a sevenfold risk for PTLD in patients after lung transplant.⁵¹ Mismatches at HLA-B loci might also confer greater risk for PTLD after renal transplantation.^{52,53} HLA-A1 carriers seem to be also at greater risk of developing EBV-related PTLD, with highest incidence being seen in HLA-A1 homozygotes, whereas HLA-A2 homozygotes are at lower risk.⁵⁴

Clinical features

The clinical signs in PTLD are nonspecific and variable, making its diagnosis challenging. Involvement of the allografted tissue can cause declining organ function; it may be the initial presenting symptom.^{55–57} For example, kidney transplant recipients with allograft involvement often present with renal dysfunction or signs of ureteral obstruction (ie, hydronephrosis) and fever.^{56,58}

Further signs of PTLT depend on the involved organs and therefore can be highly variable. Signs of PTLT can range from isolated hepatitis, lymphoid interstitial pneumonitis to infectious mononucleosis-like syndrome with fever, peripheral lymphadenopathy, and hepatitis. The gastrointestinal tract is also frequently involved; signs and symptoms such as diarrhoea and bleeding may also lead to the diagnosis of PTLT. Less common sites of involvement are the oral cavity, skin, and subcutis.

Other signs that should trigger awareness of PTLT may be more unspecific such as unexplained fever or lymphadenopathy²⁴ or hemophagocytic lymphohistiocytosis, but also more localized symptoms such as headache or confusion in case of central nervous system (CNS) involvement.^{59,60} Of all PTLT cases, primary CNS (PCNS) involvement occurs in ~5%–15%, much more frequent as the *novus* PCNS lymphoma.⁶¹ The most fulminant presentation is a diffuse systemic disease that resembles septic shock.²⁴ In laboratory tests, cytopenia, elevated lactate dehydrogenase, or detection of monoclonal protein can indicate manifest PTLT.⁶²

EBV monitoring and preemptive therapy

Quantitative polymerase chain reaction (PCR) is recommended for detecting and measuring EBV-DNA load in peripheral mononuclear blood cells, plasma, or whole blood.⁶³ It is considered as the method of choice in the early phase after HSCT. In HSCT, monitoring of EBV-DNA load is strongly recommended in all patients except in those with non-T-cell depleted matched related donor HSCT without EBV IgG sero-mismatch.^{30,53} Weekly EBV-PCR screening should start at day of HSCT for at least 3 months after HSCT. Patients with haploidentical HSCT, patients with GvHD, or patients who experienced EBV reactivation should be monitored longer. Also in SOT, monitoring of EBV viral load by PCR identifies patients at risk for developing PTLT. However, an internationally accepted cutoff of EBV-DNA burden for predicting increased risk for the development of PTLT is still not established. There is no consensus at which threshold one should initiate preemptive treatment.⁶⁴ Of note, a negative EBV-DNA load makes an EBV-associated PTLT less likely.^{65,66}

In an ongoing PTLT, the dynamic of EBV-DNA load in peripheral blood has been shown to correlate with the patient outcome. Declining levels are seen in clinical and radiological resolution of PTLT, whereas an increase in the viral DNA load is seen in progressive disease.^{67,68} Thus, measuring circulating EBV levels at regular base represents

an effective, noninvasive tool for the assessment of tumor burden and treatment efficacy.⁶⁹ In PTLT patients receiving anti-CD20 antibody, a rapid decline in EBV-DNA load is seen. This decline is independent of clinical response and is mainly due to the clearance of B cells.⁷⁰ Therefore, caution should be taken during interpretation of EBV-DNA burden in peripheral blood under B-cell depleting therapies. Once EBV reactivation occurs and PTLT is suspected, further investigations such as imaging studies to identify lymph node enlargement or organ involvement should be undertaken to exclude manifest PTLT, and preemptive measures should be made.

The type and dose of immunosuppressive therapy being the most modifiable risk factor, strategies to prevent EBV-associated PTLT target the recovery of the immune surveillance, especially T-cell function, by adjusting the immunosuppression to control the EBV-infected B-cell proliferation.

Reduction of immunosuppression (RIS) should be the initial step. In order to minimize the drawback consisting of increased risk of graft rejection in SOT recipients or graft versus host disease in HSCT patients, RIS should always be performed in close and multidisciplinary coordination with the transplant team.⁷¹

Preemptive rituximab

Styczynski et al⁶⁴ reported in their review a success of 90% (306/341 patients) in preventing EBV-associated PTLT after preemptive therapy of EBV-viremia with rituximab in patients after HSCT. Preemptive rituximab treatment of PTLT is implemented in ~80% of European HSCT centers.⁷² Application of 1–2 doses of 375 mg/m² rituximab is common.

Choquet et al² conducted a prospective single-center study on patients (n=299) after heart transplantation, treated with the same immunosuppressive regimen, and monitored by repetitive EBV-DNA load measurements in peripheral blood, setting an internal cutoff and guiding their therapy according to the EBV levels. As the first step, immunosuppression was tapered if EBV viral load was >50,000 copies/mL or EBV primary infection was present. If no response was observed, patients received preemptive rituximab. In comparison with the historical data, this study showed an effective prevention of EBV-associated PTLT by closely monitoring the EBV load and taking preemptive measures.²

The limitation of this approach is the induction of B-lymphocyte depletion for ~6 months, leading to infection susceptibility. It does not restore the cellular immunity against EBV and thus does not provide long-term control of

EBV-triggered B-cell proliferation.⁷³ Thus, in SOT patients, who are likely to take immunosuppressive drugs for life, repeated EBV reactivation must be considered upon recovery of B cells.

Preemptive adoptive immunotherapy

Adoptive transfer of autologous or allogeneic EBV-specific cytotoxic T lymphocytes (EBV-CTLs) has been investigated in several studies both in preemptive and in therapeutic settings with positive results.^{74–78} These specific T lymphocytes are isolated from either EBV seropositive stem cell donors or third-party donors and are expanded *in vitro*.

After SOT, autologous EBV-CTLs have prevented PTLD in high-risk patients.^{76,77} After HSCT, promising results were obtained in the preemptive setting: the use of donor EBV-specific CTLs prevented PTLD in all patients.^{75,78} Styczynski et al⁶⁴ found an overall response rate (ORR) of 94.1%.

The limitation in most clinical settings are the duration of the *ex vivo* expansion of these specific cells of 3–4 weeks and the high costs. Strategies to rapidly generate EBV-specific CTLs have been developed, such as overnight stimulation of donor CTLs with EBV-specific peptides and selection of antigen-specific T-cells or implementation of a third-party bank with HLA-type EBV-CTLs.^{79,80}

Preemptive antiviral therapy

Whether antiviral agents (acyclovir and ganciclovir), primarily used as cytomegalovirus prophylaxis, prevent PTLD development is also being discussed. The EBV-transformed cells do not express thymidine kinase, which is required for metabolization of the antiviral drug in the active form. It is not clear whether the ongoing active EBV replication also has a role in the development of PTLD. Funch et al retrospectively reported a strong association between freedom from PTLD and prophylactic aciclovir or ganciclovir administration in 100 pediatric patients after liver transplant compared with 375 matched controls. However, except a few reported cases of PTLD which failed to respond to conventional therapy, there is insufficient data and evidence of efficacy and safety of antiviral drugs outside clinical trials.^{71,81}

Diagnosis

Once PTLD is suspected, histopathological examination with adequate immunohistochemical staining of the specimen is essential to confirm the diagnosis of PTLD and for the appropriate classification.²³ Thus, obtaining adequate material by core or excision biopsy of tumor tissue is fundamental. Fine needle aspiration should only be performed in case of

no other option, and flow cytometric immunophenotyping has to be performed in addition.

One recommended basic immunohistochemistry panel includes staining against CD3, CD5, CD10, BCL6, BCL2, IRF4/MUM1, CD20, CD79b, PAX5, Ki67, and kappa and lambda light chains. Under certain circumstances, further evaluation (ie, ALK) may be needed.⁸²

EBV association should be determined in every tissue sample. It can be detected by immunohistochemistry for LMP1. This method is sufficient for Hodgkin lymphoma, because this lymphoma expresses the latency type 2. *In situ* hybridization targeting EBV-encoded RNA is more sensitive than immunohistochemistry and is recommended if EBV LMP1 is negative.⁸³ High-grade lymphomas frequently do not express LMP1; therefore, EBV-encoded RNA *in situ* hybridization is required in these cases.⁸⁴

The detection of EBV DNA in blood is not a diagnostic criterion for EBV-associated PTLD and cannot replace tissue biopsy.⁶⁴

The initial pretreatment work-up should include:

- Physical examination and evaluation of performance status.
- Baseline blood chemistry (CBC with differential, metabolic panel, LDH) and virology (human immunodeficiency virus, hepatitis B virus, and hepatitis C virus).
- EBV viral load by quantitative PCR in peripheral blood.
- Assessment of the function of the transplanted organ, most appropriately directed by the transplant physician.
- Completion of staging according to the Ann Arbor classification with imaging tests.
- Echocardiography if therapy with anthracycline/anthracenedione-containing regimen is being considered.

As for other fluorodeoxyglucose avid lymphomas, ¹⁸F-fluorodeoxyglucose-PET/CT is standard in pretreatment evaluation and response assessment in PTLD.^{85–88} Due to possible fatal complications of chemotherapy, comorbidities, performance status, and life expectancy should be assessed for all patients. Currently, there are no validated scores available for the assessment of comorbidities or outcome of patients with PTLD. However, scores and prognostic indices developed for comorbidity assessment in SOT and HSCT, such as hematopoietic cell transplant-comorbidity index (HCT-CI), Charlson Comorbidity Index, Adult Comorbidity Evaluation-27 (ACE-27), and the Eastern Cooperative Oncology Group (ECOG) scale of performance status measuring the impact of the disease on a patient's daily living, are reasonable options to objectivate the patients' status.⁸⁹

According to the clinical presentation, some patients may need bone marrow examination, imaging of CNS, and lumbar puncture. Staging of PTLD should be done according to the Ann Arbor staging system.⁸² The International Prognostic Index can be used as a reliable predictor of outcome in patients with PTLD.⁹⁰ In the analysis of the cohort of the international phase II PTLD-1 trial, Trappe et al found that the most important prognostic factors that correlated with the outcome and overall survival, respectively, were ECOG, age, response to rituximab, and thoracic involvement. In this study, ECOG >2 was associated with treatment-related mortality (TRM). They also showed that the International Prognostic Index score has practical advantages and, as mentioned earlier, is a reliable predictor of outcome.^{91,92}

Management and outcome

The management of PTLD is intended to be curative of this life-threatening disease without jeopardizing the function of the allograft. The main aims of the therapy are to restore cellular immunity in a sequential approach and if necessary to reduce the tumor burden.^{71,93} Due to the heterogeneity of PTLD, treatment recommendations are mainly based on small, mostly retrospective studies. Thus, although guidelines have been published, there is no consensus treatment model.

Diagnosis, classification, and management of PTLD are very challenging due to nonspecific clinical manifestation, heterogeneous pathological presentation, and lack of treatment algorithms. Treatment of PTLD also needs to take into account comorbidities and functional impairments of other organs due to long-lasting organ dysfunction prior to SOT and due to aggressive chemotherapies prior to HSCT. A management plan should be agreed by a core multidisciplinary team of experienced physicians, which should include transplant physicians, hemato-oncologists, histopathologists, and radiologists with particular experience of treating solid organ transplant patients and aggressive lymphoproliferative disorders. In some cases, the team may require input from transplant surgeons, radiation oncologists, microbiologists, and palliative care team.

Treatment approaches depend on the PTLD subtype, the type of transplantation, and the performance status of the patient. RIS should be the first step whenever feasible. As mentioned earlier, early lesions are characterized by polyclonality with no signs of malignancy. RIS may be a sufficient treatment strategy in this early phase.

Polymorphic and monomorphic lesions represent the continuum of the disease. However, polymorphic lesions are less aggressive. Thus, adding only rituximab in CD20-positive

PTLD is feasible, avoiding unnecessary toxicities. Monomorphic lesions necessitate a more aggressive approach and a combination of rituximab (if CD20-positive) with chemotherapy according to the histological findings. In light of these three major factors – PTLD subtype, patient's performance status, and type of transplant – a sequential approach is preferred by most experts. The treatment algorithm used in our center is given in Figure 1.

Outcome of PTLD also depends on the aforementioned major factors. In one large case analysis conducted by Styczynski et al,⁹⁴ patients with high-risk HSCT showed an overall mortality rate due to PTLD of 30%. The probability of overall survival at 3 years was 47.3%.⁹⁴ Among patients with PTLD after SOT, a 3-year overall survival was 62% and the 3-year progression-free survival was 57%.⁹⁵

RIS

First step of treatment for all forms of PTLD is the RIS.^{71,96–98} Before RIS is initiated, the consequence of transplanted organ loss has to be assessed together with the transplant physicians. In patients, in whom immunosuppression cannot be reduced due to potentially fatal loss of the transplant organ, alternative therapies should be promptly initiated.

For the majority of patients, once PTLD is suspected or diagnosed, immunosuppression can be reduced to the lowest tolerated levels (regarding the function of the graft usually by 25%–50% of baseline of immunosuppressive treatment and 50%–75% of baseline in heart or lung SOT) under the guidance of the transplant team. Importantly, RIS without concomitant immunosuppressive chemotherapy leads to acute allograft rejection in ~40% of patients.⁹⁸

A response to RIS is usually seen within 2–4 weeks and can be achieved in up to 45%.⁹⁸ With 10% clinically meaningful responses, this rate is much lower in studies analyzing only monomorphic PTLD.^{97,99,100} If the PTLD completely resolves with RIS, no further treatment may be required. After HSCT, RIS seems to be less efficient compared with SOT.

Waiting for response to RIS is clinically often not feasible, especially in patients with known adverse features associated with poor response to RIS such as raising LDH under RIS, organ dysfunction, and multiorgan involvement.⁹⁷

Further therapy should be promptly initiated if clinical and histological findings suggest progressive disease or if the tumor fails to respond within 3–4 weeks after the initiation of RIS.⁷¹ In a phase II prospective study, Swinnen et al⁹⁹ evaluated a sequential approach to therapy in 16 evaluable patients after SOT. If no complete remission (CR) was achieved after RIS, further therapy (in this case interferon

Figure 1 Treatment algorithm of PTLT.

Notes: In patients who relapse late after 2 years, the initial treatment should be repeated. In patient who relapse early or are refractory, we recommend the carboplatin/etoposide regimen. *The category of CD20+ PTLT refers to CD20-positive non-Hodgkin lymphomas including Burkitt's lymphoma.

Abbreviations: ABVD, adriamycin/bleomycin/vinblastine/dacarbazine; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisolone; CNI, calcineurin inhibitor; CNS, central nervous system; CR, complete remission; CTx, chemotherapy; HD MTX, high-dose methotrexate; mTOR, mammalian target of rapamycin; PTCL, peripheral T-cell lymphoma; RIS, reduction of immunosuppression; RTx, radiation therapy.

alfa) was given. If no CR was achieved further, multiagent chemotherapy was applied. Only one patient achieved partial remission after RIS. Therapy with interferon alfa resulted in one CR; 67% achieved CR after chemotherapy. The regimen did not contain rituximab.⁹⁹

When combining RIS with rituximab in CD20-positive PTLT, PTLT resolved in 84% of cases. A remarkable finding is that rituximab alone without RIS-induced remission is in only 61%. Prompt RIS at the time of PTLT diagnosis was an independent prognostic factor for survival from PTLT and also for OS with a 2.8-fold risk reduction of death.⁹⁴

Rituximab

Adding rituximab increases ORR with tolerable toxicities, thus our approach is to initiate rituximab parallel to RIS for

CD20-positive poly- or monomorphic PTLTs. Rituximab may be administered as single agent or in combination (concurrent, sequential) with chemotherapy.

Several prospective phase II studies and retrospective analyses have confirmed the efficacy of rituximab therapy as single agent in CD20-positive PTLT in combination with RIS with ORRs of ~70% and CR rates up to 50%.^{70,101,102} Specific data on the outcome and survival in poly- or monomorphic types under rituximab are lacking.

In a multicenter phase II trial conducted by Oertel et al,¹⁰³ rituximab 375 mg/m² weekly, for 4 weeks consecutively, was administered in patients with PTLT after SOT. Fourteen patients have had monomorphic and three have had polymorphic PTLT. CR was induced in up to 50% of patients.¹⁰³ A similar prospective phase II study conducted by Choquet et al¹⁰⁴

showed an ORR of 44.2% with CR of 28% in patients with PTLT after SOT. Relapse occurred in 21% of cases.¹⁰⁴

A scoring system has also been proposed to identify patients with PTLT who may not respond well to RIS in combination with rituximab. The factors taken in account were age >60 years, ECOG performance status 2–4, and raised LDH. Three risk categories were identified: low-risk group (0 risk factors), intermediate-risk group (1 risk factor), and high-risk group with >1 risk factor and the 1- and 2-year survival was 100% and 79%, 36% and 88%, 50% and 0%, respectively.¹⁰¹

In a prospective phase II study, extended treatment with another course of four times weekly rituximab was performed in patients who did not achieve CR after the first course of rituximab. Higher rates of CR were achieved, without increasing toxicity, achieving an intention to treat CR rate of 60.5% and an overall survival of 42 months.¹⁰⁵

Thus, rituximab is an effective first-line therapy in CD20-positive B-cell PTLT with manageable toxicity and can be incorporated in treatment of polymorphic or monomorphic PTLT independent of comorbidities and performance status.

Combined immunochemotherapy

Patients with monomorphic PTLT can be treated with polychemotherapy. For polymorphic PTLT with high tumor burden, chemotherapy should also be considered. As TRM of polychemotherapy is high in PTLT patients after HSCT or SOT, ranging between 11% and 33%, organ function and comorbidities should be assessed as mentioned earlier to outweigh the benefits and risks of chemotherapy.^{106–108}

Most experience exists using CHOP-21 (cyclophosphamide, doxorubicin, vincristine, and prednisolone in 21-day intervals) with CR rates of 42%–66%.^{107–109} These response rates can still be achieved in patients refractory to or relapsing after rituximab.¹⁰¹

Trappe et al¹⁰⁶ published the results of a prospective multicenter phase II study (N=74; N=70 evaluable). The sequential immunochemotherapy, consisting of weekly rituximab 375 mg/m², 4 weeks, followed by four cycles of chemotherapy (CHOP-21 regimen with posttherapeutic G-CSF support) in patients who failed initial RIS and who were eligible for more aggressive chemotherapy. PTLT was of late type in 76% of cases, monomorphic in 96% of cases, and EBV associated in 44% of cases. ORR with rituximab was 60% and improved to 90% (CR 67%) after receiving subsequent chemotherapy. Approximately 50% of responders were progression free after 5 years. Under aggressive antimicrobial prophylaxis, the TRM rate was still 10.6%. The study has been revised introducing risk-stratified sequential treatment according

to the response to rituximab. Patients were stratified in two categories: those with low risk, defined as achieving CR after four cycles of rituximab alone and those with high risk, defined as nonCR after rituximab. Low-risk patients received consolidation therapy with another four cycles of rituximab, whereas high-risk patients proceeded to chemotherapy.

This approach is viewed from many experts as evidence-based standard for CD20-positive B-cell PTLT progressive after RIS outside a clinical trial and independent of EBV status.^{93,106,110}

Adoptive immunotherapy

As mentioned earlier, several small studies showed a beneficial effect of EBV-CTLs used for prevention of PTLT in high-risk patient.

The therapeutic effect of these EBV-CTLs was evaluated in one prospective multicenter phase II study.¹¹¹ The majority of patients were post-SOT (95%); all of them received various prior therapies (rituximab, chemotherapy, and antiviral) and failed to respond. After infusion of cytotoxic T-cells, the ORR was 52% with 42% CR. OS was found to be 79% at 6 months.^{111,112} An advantage of this treatment modality is avoidance of augmenting the risk of graft rejection after RIS in SOT patients. However, treatment is hampered by the complex preparation process, which is not available in all centers.

Donor lymphocyte infusion may also represent a feasible treatment option in patients after HSCT. This approach has shown an ORR of 70%. The availability is much broader than that of EBV-CTLs, but it is not recommended for patients suffering from GvHD. Donor lymphocyte infusion is associated with severe, life-threatening GvHD.^{64,113,114}

Surgery

At present, the value of surgical resection of PTLT is not validated. There are a few situations where surgery is necessary or may have a role as additional treatment modality. First, excision biopsy may be needed if core biopsy is not feasible or its results are nonconclusive and rebiopsy is needed. In this scenario, if the PTLT is localized, a complete removal of lymphoma may be done as a part of the treatment, but adequate systemic therapy according to histology, risk factors, and patient's fitness should also be given. Localized manifestation of PTLT is however very rare, and it seems mostly after SOT such as heart, lung, kidney, or liver transplant.^{71,115}

Second, in emergency situations such as persistent hemorrhage despite conservative management or colonic obstruction, surgery is necessary to stop the bleeding or avert colonic perforation. For localized manifestation of early lesions or

polymorphic PTLT (Ann Arbor stage I), surgical resection might be an option if RIS is not tolerated. Adjuvant systemic therapy with rituximab, although not evidence based, should be considered in patients with polymorphic PTLT.¹¹⁰

Radiotherapy

This therapeutic approach should be considered additionally to other treatment modalities in special circumstances such as orbital involvement, solitary plasmocytoma-like PTLT, Hodgkin and Hodgkin-like PTLT in stage I, or isolated CNS relapse.¹¹⁰ Radiotherapy also plays an important role in some emergency setting (ie, cord compression). Moreover, it can be useful in palliation of symptoms due to local complication of PTLT.^{116,117} The treatment regimen (dose and fractionation) should be similar to the de novo lymphoma protocols. In palliative situation, lower doses should be used.⁷¹

Special clinical situations

CD20-negative PTLTs, T-cell PTLTs, and PCNS PTLT should be treated according to their counterparts occurring in immunocompetent patients.⁸⁸ In CD30 T-cell lymphoma-like PTLT, brentuximab treatment was reported to be successful.¹¹⁸ This approach needs to be evaluated in larger case series of HD- and PTCL-type PTLT.

Of all PTLT cases, PCNS involvement occurs in ~5%–15%, much more frequent as the novo PCNS lymphoma. Approximately 80% of total PCNS PTLT are EBV-associated, and those with early onset is ~100%. PCNS PTLT is distinctly more aggressive than its systemic counterpart.¹¹⁹ Evens et al¹²⁰ conducted a retrospective analysis of 84 patients with PCNS PTLT in the postrituximab era. They identified some important prognostic factors such as performance status and LDH and showed that the most predictive factor for survival was response to first-line treatment.¹²⁰ There is no established treatment algorithm for PCNS PTLT. The currently used therapy approach is similar to the de novo PCNS lymphoma. The inconsistent treatment regimens and absence of prospective randomized trials make evaluation of retrospective data difficult. For patients with good performance status, systemic high-dose cytarabine or methotrexate is recommended. For those with poor performance status, whole brain irradiation should be considered. The role of CNS prophylaxis in high-risk PTLT patients is also unclear; therapeutic strategies depend on internal institutional protocols.⁸⁸

Salvage therapy

For patients with relapsed or refractory PTLT after first-line treatment, no current standard therapy options are available.

Data are based only on case reports and retrospective studies (Table 4). Oertel et al¹²¹ reported a complete response in five of nine relapsed or refractory PTLT patients treated with carboplatin and etoposide. Two patients died due to treatment-related complications. In this setting, an individual therapy concept based on the histological subtype of PTLT must be considered. As most patients present in poor clinical condition and are prone to infectious complications, the treatment plan should also incorporate these aspects. Patients with late relapse (beyond 2 years after first-line treatment) are retreated with the first-line therapy in our institution. For patients with early relapse, we use the carboplatin/etoposide schema reported by Oertel et al.¹²¹ In case of fit patients, interdisciplinary consolidation by autologous or allogeneic stem cell transplantation is discussed.

Supportive care

TRM in patients treated with combined chemotherapy is significant, 50% being caused by infections. Proper prophylaxis of these infections is a key component in the management of patients with PTLT. The usefulness of G-CSF to prevent febrile neutropenia in patients treated for solid tumors or lymphoma has been confirmed.^{122,123} A primary prophylaxis should therefore be considered in all patients with increased risk for febrile neutropenia.¹²⁴ Antibiotic, antiviral, and antifungal prophylaxis during therapy should be considered according to institutional internal protocols. Special consideration is warranted in cases of chronic viral infections such as hepatitis B and C or human immunodeficiency virus. Because of risk of reactivation, patients with hepatitis B virus should receive at least prophylaxis with lamivudine.^{71,125}

Conclusion and future perspective

With worldwide increasing transplantation rates and more effective immunosuppressants, early diagnosis and adequate treatment of PTLT will become more and more relevant. The highly variable clinical presentation and histological picture make diagnosis challenging. A close cooperation of clinicians and pathologists is important for correct diagnosis. The backbone of PTLT treatment is RIS. In CD20-positive PTLT, rituximab leads to improved outcome and therefore is the second cornerstone of treatment. However, despite these advances, mortality rate due to PTLT remains high. This is mostly due to poor performance status of the patients and insufficient options for treatment. Prospective studies testing a risk-adapted sequential treatment approach not only include response to rituximab but also other risk factors such as International Prognostic Index are under way (NCT02042391). Incorporation of

Table 4 Reported salvage regimen and outcome in patients with PTLD relapsed or refractory to first (immune)chemotherapy

	Transplant setting	PTLD type	Prior therapy	Salvage therapy	Outcome
Malhotra et al ¹²⁷ N=1	66 years, male SOT (heart) EBV IgG negative 8-year postTx	DLBCL, Ann Arbor IA	RIS + rituximab + 6× R-CHOP + radiation	2× R-ICE, 2× R-GemOx and HD-BEAC + autologous SCT	At 17 months: alive, CR, fully functional allograft
Komrokji et al ¹²⁸ N=2	36 years, male SOT (kidney–pancreas) EBV IgG positive OKT3 Tacrolimus, MMF, prednisone 21-month postTx	CNS PTLD, DLBCL	ISA: sirolimus + prednisone R + 2× ESHAP + 2× HD- MTX	Mini BEAM + autologous SCT + radiation	At 30 months: alive, CR, fully functional allograft
	52 years, male SOT (2nd kidney) EBV IgG positive Tacrolimus, MMF, prednisone 11-month postTx	Anaplastic plasmocytoma	ISA: sirolimus + prednisone 4× R weekly + 3× ESHAP	2× Mini BEAM + autologous SCT	At 31 months: alive, CR, fully functional allograft
Oertel et al ¹²¹ N=9	59 years, male SOT (heart)	DLCBL, Ann Arbor IV	RIS + 2× CHOP	4× CE	At 92 months: death not due to PTLD
	38 years, female SOT (double lung)	DLBCL, Ann Arbor IV	RIS + 1× CHOP	1× CE	Death due to intestine perforation, PTLD in PR
	59 years, male SOT (heart)	DLBCL, Ann Arbor IVE	RIS + 3× CHOP	4× CE	At 17 months: death not due to PTLD
	43 years, female SOT (lung)	DLBCL, Ann Arbor IV	RIS + 4× CHOP	3× CE	Death due to MOF, autopsy: CR
	65 years, male SOT (lung)	DLBCL, Ann Arbor IV	6× CHOP	4× CE + intrathecal MTX + cranial radiation	At 55 months: alive, CR
	46 years, female SOT (lung)	DLBCL, Ann Arbor II	RIS + 3× CHOP	4× CE	At 39 months: alive, CR
	62 years, male SOT (heart, renal)	MCL, Ann Arbor IV	RIS + 2× CHOP	2× CE	Death due to PTLD
	53 years, female SOT (heart)	DLBCL, Ann Arbor IV	RIS + 3× CHOP + 1× CBCDA/VPI	1× CE	Death due to PTLD
Trappe et al ¹⁰¹ N=2	40 years, female SOT (heart) 44 years, female SOT (liver) 2.3-month postTx	Atypical Burkitt, Ann Arbor IIB MZL, Ann Arbor IV E	RIS + 4× R + 6× CHOP 6× R + 1× CHOP	2× CE + abdominal radiation Leukeran (16 months) + 6× bendamustin	At 9 months: alive, CR Death due to PTLD
	45 years, female SOT (heart) 12.5-month potsTx	DLBCL, Ann Arbor II	4× R + 1× CHOP	Ixoten (2 months)	Death due to PTLD
Dierickx et al ^{82,88}	36 years, female SOT (2nd kidney) 12-year postTx	EBV-DLBCL, Ann Arbor IVA	RIS + R + R-CHOP	R-DHAP + HD- CTX + autologous SCT	At 36 months: alive, CR, fully functional allograft

Abbreviations: CE, carboplatin/etoposide; R-CHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisolone; CNS, central nervous system; CR, complete remission; CTx, chemotherapy; DHAP, dexamethasone/high-dose cytarabin/cisplatin; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein–Barr virus; HD-CTX, high-dose chemotherapy; HD-BEAM, high-dose carmustin/cytarabine/etoposide/melphalan; R-ICE, rituximab/ifosfamid/carboplatin/etoposide; ISA, immunosuppression adjustment; MOF, multiorgan failure; MZL, marginal zone lymphoma; PTLD, posttransplant lymphoproliferative disease; R, rituximab; RIS, reduction of immunosuppression; SCT, stem cell transplantation; SOT, solid organ transplantation; Tx, transplantation; R-GemOx, rituximab/gemcitabine/oxaliplatin; HD-BEAC, high-dose carmustine, etoposide, cytarabin, cyclophosphamide; ESHAP, etoposide, methylprednisolone, cytarabin, cisplatin; HD-MTX, high-dose methotrexate; CBCDA, carboplatin.

new, less-toxic therapies such as inhibitors of the mammalian target of rapamycin in treatment algorithms might also help us to improve future treatment and outcome of PTLD.^{126,127}

Disclosure

LPM has received congress registration fees and reimbursement of travel costs from Astellas, Janssen, Sanofi, Gentium, Jazz Pharmaceuticals, and Gilead. He has received honoraria for lectures from Novartis, Celgene, and Pfizer. He has acted as a consultant for Celgene and CTI Life Sciences. KL, CMT, and TW report no conflicts of interest in this work.

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