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Post-transplant lymphoproliferative disorder in view of the new WHO classification: a more rational approach to a protean disease?

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Abstract

Post-transplant lymphoproliferative disorders (PTLDs) are serious, life-threatening complications of solid-organ transplantation (SOT) and bone marrow transplantation leading to a high mortality (30–60%). PTLD represents a heterogeneous group of lymphoproliferative diseases. They become clinically relevant because of the expansion of transplantation medicine together with the development of potent immunosuppressive drugs. Although the diagnostic morphological criteria of different forms of PTLD are commonly known, rapid and correct diagnosis is not always easy. Because of the limited number of clinical trials, a consensus is lacking on the optimal treatment of PTLD. This review focuses on incidence, risk factors, clinical picture of the disease and diagnostic tools including histopathology relating to the new classification introduced in 2008 by the World Health Organisation (WHO) and treatment of PTLD.

Keywords: EBV; histopathology; PTLD; SOT; transplantation

Introduction

The term 'post-transplant lymphoproliferative disorder' or disease (PTLD) was first introduced in 1984 by Starzl [1]. Today, it represents a heterogeneous group of lymphoproli-

Table 1. The incidence and location of PTLD in solid-organ transplant recipients

Type of transplanted organ	Location and frequency [%]							References
	Kidney	Lung	Liver	CNS	Lymph nodes	GI tract	Disseminated	
Kidney	10.3–32	4.4	4.9	11.7	9.5	15.3	14	[4–7,16,23,32]
Liver		4.2	21.8–33	4.2	9.7	12.1	13.3	
Heart	0.6	16.0	8.9	4.0	4.4	14.3	14.5	
Lung and heart–lung	1.4	50–80	4.8	3.4	2.1	4.8	10.3	

ferative diseases, ranging from Epstein–Barr virus (EBV)-associated polyclonal proliferation to highly aggressive monomorphic proliferations, such as diffuse large B-cell lymphoma (DLBCL) [2,3]. The reported incidence of PTLD is very variable as is its related mortality (30–60%). The clinical picture, intensity of immunosuppression (IS), primary and co-existing diseases and PTLD location are also quite variable. For all these reasons, the diagnosis of PTLD is not easy; moreover, the pathologist frequently faces unusual cases of lymphoid proliferations that do not fit any recognized PTLD type. Therefore, WHO introduced in 2008 a new PTLD classification, aimed at improving diagnosis and consequently treatment modalities. So far, immunosuppression reduction (IR) is the only accepted first-line therapy; however, poor response in many types of PTLD requires other approaches such as antiviral therapies, chemotherapy, monoclonal antibodies, proliferation signal inhibitors (PSIs) and finally surgery.

Incidence and risk factors

The incidence of PTLD, ranging from 1% to 20%, clearly relates to the type of transplanted organ, IS, underlying disease, age, viral infections including EBV, cytomegalovirus and hepatitis C virus (HCV), and length of post-transplant follow-up. Although the occurrence decreases after the first post-transplant year, the cumulative incidence increases with the time elapsed since transplantation. The highest incidence from 5% to 20% is reported following lung and intestinal transplantation; in contrast, renal transplant recipients (RTRs) have an incidence of 1–3% [4,5]. In liver transplant recipients, the occurrence ranges from 2% to 10%, from 2–3% in adults to 10% in children [4,6,7] (Table 1).

Induction IS using anti-T-cell antibodies such as OKT3® (Janssen-Cilag, New Brunswick, USA) or Thymoglobulin® can lead to an increased risk of PTLD. In contrast, ATG® (Fresenius Biotech GmbH, Germany) or interleukin 2-receptor (IL-2R) antibodies induction (Simulect®, Novartis Pharma AG, Basel, Switzerland) do not increase PTLD risk [4,8–10]. On the other hand, the treatment of rejection episodes during the first post-transplant year with OKT3 or ATG enhances the PTLD risk in patients who did not receive antibody induction. Moreover, in patients who also received antibody induction, rejection therapy with OKT3 or ATG adds to the already increased lymphoma risk [4]. The PTLD risks associated with the use of the calcineurin inhibitors (CNI) tacrolimus (Prograf®, Astellas Pharma Europe B.V., Leiderdorp, The Netherlands) and cyclosporin A (Neoral®, Novartis Pharma AG, Basel, Switzerland), and PSI: sirolimus (Rapamune®, Pfizer, New York, USA) and everolimus (Certican®, Novartis Pharma AG, Basel, Switzerland) remains uncertain [11–13]. It is, however, clear that the intensity of IS, rather than the use of any particular agent, is critical for development of PTLD.

EBV infection is a risk factor and a cause of PTLD present in more than 80% of B-lymphocyte phenotypic disorders and, less commonly, in T-lymphocytic proliferations [9,14]. After infection, B cells incorporate EBV DNA into the cellular genome, decreasing the rate of apoptotic cell death through bcl-2 induction and stimulating extensive proliferation of B cells, possibly leading to lymphoblastoid transformation [10,15]. EBV-seronegative recipients receiving transplants from EBV-seropositive donors are at particular risk for PTLD development. Paediatric recipients who are very frequently EBV seronegative before transplantation are especially prone to develop PTLD.

Cytomegalovirus and HCV are also, albeit less, involved in the pathogenesis of PTLD [16–18]; however, their role as risk factors for PTLD is controversial, as is that of herpes simplex or simian virus infections [19].

Human leukocyte antigen (HLA) matching is another risk factor in the pathogenesis of PTLD in RTRs; HLA-B or HLA-DR mismatches especially seem to be critical, independently of the type of IS. The number of HLA mismatches parallels with an increased risk of PTLD. HLA-B mismatches increase the risk of lymphoma in the kidney, whereas HLA-DR locus mismatches are exposed to a higher risk of non-Hodgkin lymphoma, namely located in the kidney and the central nervous system [20,21].

Clinical picture

The clinical picture of PTLD differs from that of lymphomas observed in the general population. Aggressiveness and outcome of the PTLD depends on the histological type and/or the supplementary fact that transplant recipients are more susceptible to develop complications after lymphoma treatment.

Symptoms may be mild, such as fever, mononucleosis-like syndrome, lymphadenopathy, recurrent infections of unknown origin resistant to antibiotics or severe organ dysfunction. The variable manifestation of PTLD depends on numerous factors, including the type of transplanted organ or IS used, histopathology and time elapsed since transplantation. The incidence during the first year varies depending on the reported series, and one must be cautious,

as the mean time to diagnosis changes with the duration of follow-up. It has been shown that the PTLD incidence at 1 year was only one-fifth of the cumulative 10-year incidence and that the median time of occurrence reaches about 5 years [4]. A case of PTLD observed as early as 15 days after kidney–pancreas grafting has been reported [22]. The location of the lesions also relates to the type of transplant and the time span elapsed since transplantation. In lung recipients, more than 50% of all PTLDs develop during the first post-transplant year in the allograft itself in contrast to other organs [4,23]. The large European registry of over 200 000 SOT recipients estimated that the respective allograft was affected in 10.3% of kidney, 16% of heart, 21.8% of liver and 42.7% of heart–lung recipients (Table 1) [4]. The exact mechanism leading to a preferential allograft localization remains unclear today; chronic antigen stimulation, passenger lymphocytes in the graft or development of lymphoma from donor lymphocytes have all been mentioned in relation to this.

Other frequent sites of PTLD include the gastrointestinal tract (jejunum more often than colon), lymph nodes and central nervous system. The involvement of these locations also varies between types of transplanted organ [4] and depends on the age of the recipient too. Skin and tonsils are considered rare PTLD locations in adults, whereas in children, the lymph nodes of the Waldeyer's ring and tonsils are very common target organs. Regardless of the graft type, patients with lymph node localization have a relatively good outcome; disseminated disease in contrast has a poor prognosis.

Diagnosis

PTLD often presents in a nonspecific way. Medical history, thorough physical examination and different endoscopic and imaging techniques are crucial in making a prompt diagnosis. Fluorodeoxyglucose-positron emission tomography has proved superior to conventional methods of PTLD visualization. The final diagnosis is always based on histopathology.

Assessment of EBV DNA load is important for early identification and appropriate monitoring of high-risk recipients [24]. Detection of an increased EBV load alone is not always predictive of PTLD, a fact that may be explained by the concomitant increase in EBV-specific cellular responses. Because there are no established threshold values of the number of EBV DNA copies, the dynamics of increasing EBV DNA levels is a helpful guide to decrease IS or start cytotoxic T-cell-based or anti-CD20 therapies [25]. Some authors have suggested that the detection of increased EBV DNA load in combination with reduced EBV-specific T-cell counts could allow a more precise prediction of the risk of PTLD development, particularly in EBV-seronegative recipients [26]. Additionally, the EBV particles can be detected in examined tissues by immunohistochemistry (IHC) and molecular methods including in situ hybridization [27]. Detection of antibodies against the EBV latent membrane protein 1 (LMP1) or EBV nuclear antigen 2 may be applied in frozen or paraffin-embedded tissues.

Polymorphisms of interferon-γ, tumour necrosis factor-α and IL-2 related to a low cellular immune response, as well as increased levels of IL-10 acting as an autocrine growth factor for EBV-transformed B cells are associated with an increased risk of PTLD. They all represent other measures that could potentially supplement diagnostics of EBV-related PTLD [28–30].

Histopathological classification

As the morphological picture of PTLD is variable, several classifications of PTLD have been put forward. According to the newest WHO classification, introduced in 2008, four basic histological types of PTLD have been identified [31].

Typical morphological picture of different forms of PTLD

Plasmacytic hyperplasia (PH), mononucleosis-like PTLD, and polymorphic PTLD (P-PTLD) are specific for transplant recipients, whereas the other types can also be diagnosed in immunocompetent individuals.

1. Early lesions. The architecture of the involved tissue in PH is generally retained, and nodal sinuses are preserved. Reactive follicles in the periphery of the lymph node are often seen. The large number of polyclonal plasma cells (VS38c+, κ+, λ+) may be found as single cells, small groups or large sheets (Figure 1A–C) together with lymphocytes and occasional immunoblasts.

The microscopic picture of the infectious mononucleosis-like PTLD typically appears with the expansion of the T zone with numerous immunoblasts and plasma cells (Figure 1D).

Cytologic atypia in both types of early lesions is minimal. Early PTLD is usually diagnosed in children, young adults and patients with primary EBV infection [31,32].

2. P-PTLD. The architecture of involved tissues is affected by an infiltrate consisting of various cells: small and medium-sized lymphoid cells, centrocyte-like cells, plasma cells and immunoblasts. Atypical lymphoid cells and cells resembling Reed-Sternberg cells (RS) may be observed. It is the most common type in children, usually related to primary EBV infection [33] (Figure 1E).

3. Monomorphic PTLD (M-PTLD) includes all T/natural killer neoplasms and most B-cell lymphomas.

4. Classical Hodgkin lymphoma (HL) is diagnosed according to the same criteria as in immunocompetent patients. The most frequent form is of mixed cellularity [34]. Classic RS cells are seen in a reactive inflammatory background (small lymphocytes, histiocytes, plasma cells, eosinophils). Diagnostic cells are typically CD30 and CD15 positive and CD20 marker variable.

Typical and common forms of PTLD

The first three types of PTLD are relatively common and usually develop with the typical morphological features

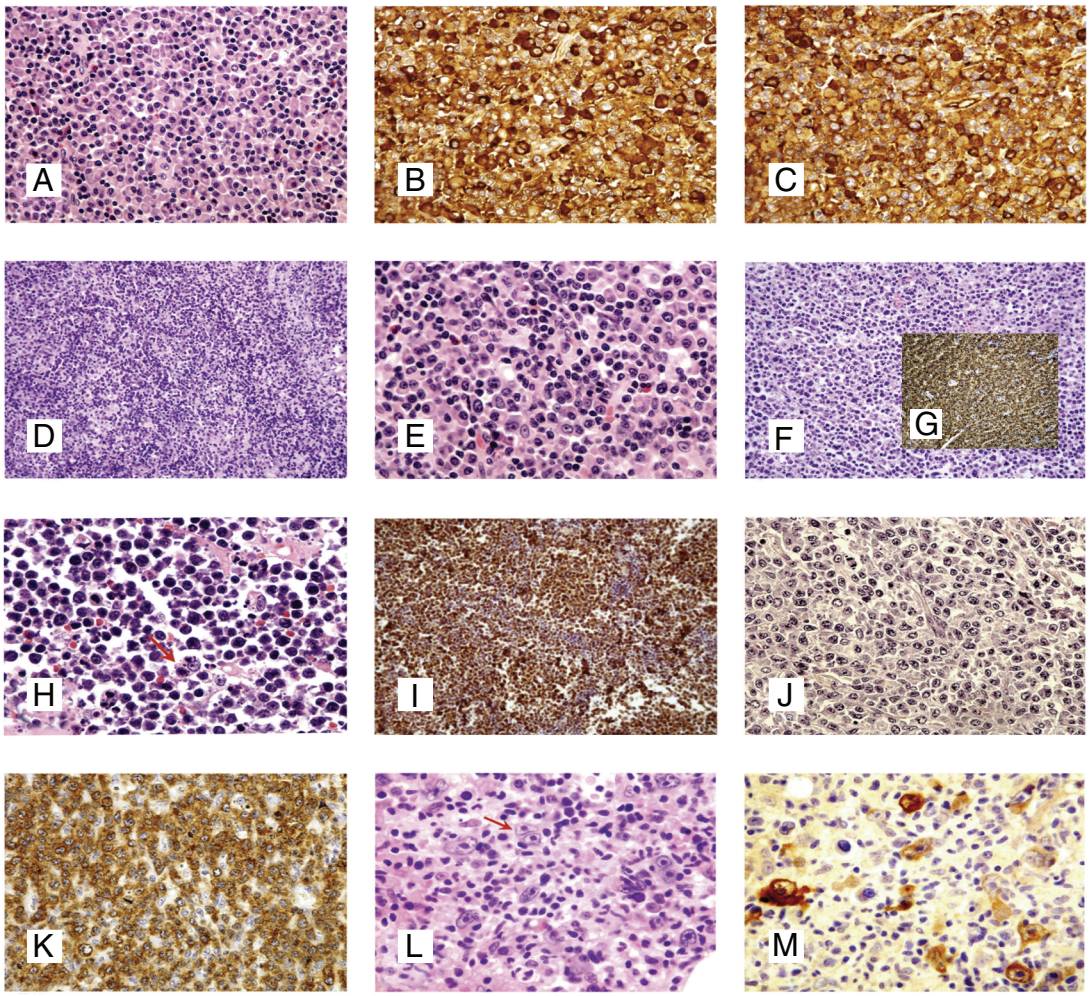


Fig. 1. Histopathology of PTLD. (**A**) PH. Haematoxylin and eosin (H&E) stain. Objective magnification ×40. Large number of plasma cells admixed with small lymphocytes and singular eosinophils. (**B**) PH. Immunohistochemical stain with kappa immunoglobulin light-chain antibody. Objective magnification ×60. (**C**) PH. Immunohistochemical stain with lambda immunoglobulin light-chain antibody. Objective magnification ×60. (**D**) Infectious mononucleosis-like PTLD. H&E stain. Proliferation of small lymphoid cells, plasma cells and immunoblasts. Objective magnification ×10. (**E**) P-PTLD. H&E stain. Many plasma cells, immunoblasts (large cells with vesicular nuclei and clearly visible centrally located nucleoli, singular eosinophils). Objective magnification ×60. (**F**) M-PTLD, DLBCL. H&E stain. Atypical large cells with large irregular nuclei, abundant cytoplasm, and two to three peripherally located nucleoli. Objective magnification ×20. (**G**) M-PTLD, DLBCL. Immunohistochemical stain. Positive reaction of lymphoma cells with CD20. Objective magnification ×20. (**H**) M-PTLD, Burkitt's lymphoma. H&E stain. Medium-sized B cells with multiple inconspicuous nuclei and scattered tingible-body macrophages containing cellular debris. Objective magnification ×60. (**I**) M-PTLD, Mantle cell lymphoma. Immunohistochemical stain with cyclin D1 (SP4). Typical nuclear staining. Objective magnification ×20. (**J**) M-PTLD, PTCL, unspecified. H&E stain. Polymorphic medium-sized and large cells, many with irregular vesicular nuclei and distinct nucleoli. Objective magnification ×40. (**K**) M-PTLD, PTCL, unspecified. Positive immunohistochemical stain with CD3 antibody. Objective magnification ×40. (**L**) M-PTLD, DLBCL, Hodgkin-like. H&E stain. Objective magnification ×60. Numerous Hodgkin-like and RS-like cells, with abundant cytoplasm, multilobular nucleus and one to two prominent nucleoli. (**M**) M-PTLD, DLBCL, Hodgkin-like. Immunohistochemical stain. Objective magnification ×60. Positive reaction with EBV (LMP1).

described above. More than 85% of PTLDs derive from B cells, 14% from T cells and about 1% from natural killer cells [31,35–37].

Among M-PTLDs, the most common is DLBCL. The term 'monomorphic' does not reflect similarity of the cells, which are often different in shape and size. RS-like, multinucleated and plasmacytoid forms may be encountered. According to the 2008 WHO classification, DLBCL is classified as a centroblastic or immunoblastic variant. Centroblastic DLBCL presents with diffuse proliferation of atypical large cells with large irregular nuclei and two to three nucleoli located peripherally (Figures 1F and G). The immunoblastic variant has large neoplastic cells with large nuclei and centrally located prominent nucleoli. IHC distinguishes two main groups of DLBCL: those originating from germinal centre cells and those of non-germinal-centre phenotype. The proliferation index of DLBCL is high; Ki-67 exceeds 40% of lymphoma cells [38].

Other types of B-cell lymphomas such as Burkitt's lymphomas are diagnosed less frequently [39,40]. Burkitt's lymphoma presents with the same pathomorphology as in immunocompetent patients: monomorphic medium-sized B cells infiltrate with extremely high mitotic activity, often with the presence of many tingible-body macro-

phages, containing cellular debris ('starry sky' pattern) (Figure 1H).

Another group of M-PTLDs are the plasma cell neoplasms: multiple myeloma or extramedullary plasmacytoma, which are morphologically and immunophenotypically identical to the forms in immunocompetent patients [16,41,42].

Rare forms of PTLD

Although common in immunocompetent patients, some types of lymphoma such as mantle cell lymphoma develop rarely in transplant recipients. Centrocyte-like cells with irregular nuclei infiltrate the lymph node diffusely, and IHC shows a positive reaction with cyclin D1 (SP4) (Figure 1I) [37]. The T/natural killer-cell lymphomas are rare forms of PTLD. They develop late after transplantation, usually in extranodal sites, and are more aggressive than B-cell neoplasms [31,43]. Peripheral T-cell lymphoma (PTCL), not specified, and hepatosplenic T-cell lymphoma belong to the most frequent types (Figure 1J and K) [44].

'Mixed' PTLD

Different morphological types of PTLD can be observed in the same patient. Overlapping forms of PTLD or cases in which histological changes are differentially advanced in various organs may be diagnosed. Reactive PH in one tonsil and a more advanced form of P-PTLD in the second or partial involvement of the tonsil by P-PTLD and partial by classic DLBCL have been described [37,45]. It should be emphasized that final diagnosis corresponds always to the more aggressive lesion.

Atypical PTLD

Atypical forms of PTLD are morphologically or immunophenotypically different from classical forms and are therefore difficult to classify. An example is PH with depletion of lymphocytes diagnosed in the lymph node of a 54-year-old after liver transplant. The node architecture was partially effaced with sinus dilatation and fibrosis. It was accompanied by a decreased number of lymphocytes, especially of T phenotype. Numerous polyclonal plasma cells were present. The course of the disease was rapidly progressive, and the patient died due to generalized infection and systemic lymphadenopathy [46].

Certain types of PTLD initially do not fit a classification and demand complementary IHC or molecular techniques as showed in one of our RTR [47]. His bone marrow biopsy revealed diffuse dense infiltration formed by two populations of lymphoid cells. The first consisted of small- to medium-sized cells with slightly irregular nuclei and the second of large polymorphic RS-like cells, with a multilobular nucleus and prominent one to two nucleoli (CD30+, EBV/LMP1+) but negative for CD15 and B-cell markers (Figure 1L and M). There was also no fibrosis and no reactive inflammatory background characteristic for HL; therefore, the generally accepted diagnostic criteria of HL were not fulfilled. Because basic IHC stains for B lymphocytes were negative, B-cell Hodgkin-like lymphoma was also excluded, and anaplastic large-cell lymphoma was firstly diagnosed. However, the IHC stains for BOB1 and OCT2 confirmed the diagnosis of B-cell Hodgin-like lymphoma (WHO 2001), currently DLBCL (WHO 2008).

Analysis of the literature shows that the differences between WHO 2001 and 2008 classifications are few and lead to the maintenance of the four main categories of PTLD with small changes in their terminology. Two significant changes concern Burkitt-like variant of Burkitt lymphoma and HL-like PTLD. Many of Burkitt-like lymphoma falls into the new category: unclassifiable B-cell lymphoma, with features intermediate between DLBCL and Burkitt lymphoma. HL-like PTLD, belonging to category 4 of WHO 2001 classification, is currently considered DLBCL and belongs to M-PTLD group. It may be microscopically identical to classical HL, but large RS-like cells, active forms of immunoblasts, are LCA, CD30 and B-cell marker positive and CD15 negative [31,48–50]. This change greatly impacts on the choice of treatment, which is different for each type of lymphoma. The possibility of applying anti-CD20 antibodies gives the chance of successful treatment in case of B-cell origin lymphomas.

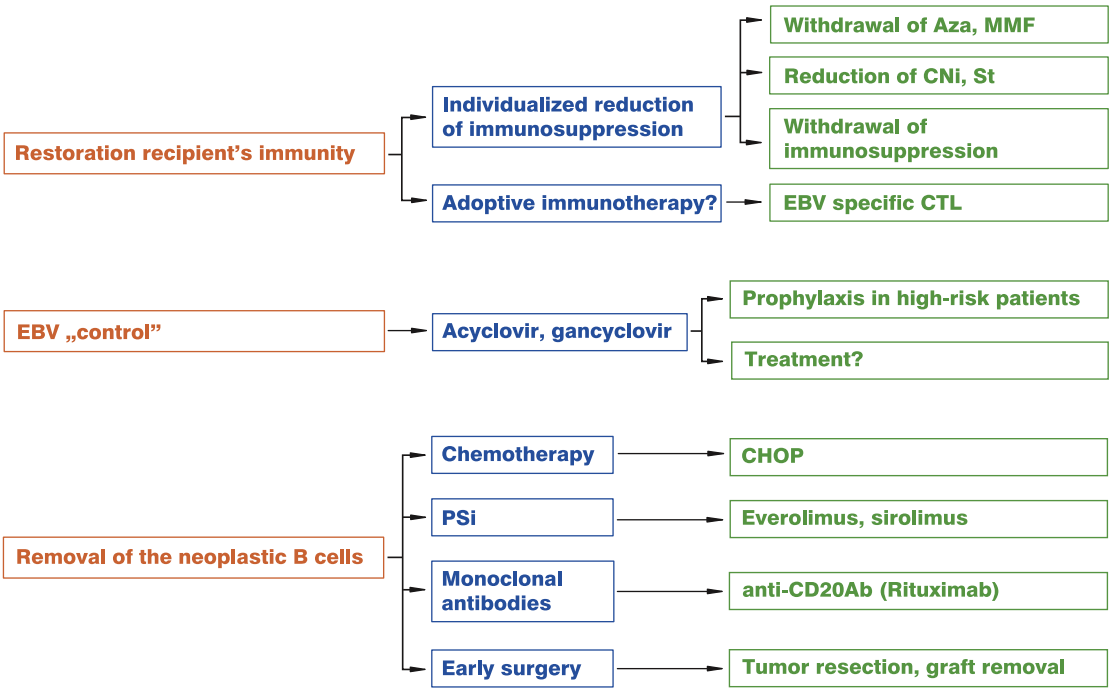
According to the newest classification, indolent small B-cell lymphomas such as follicular lymphomas and mucosa-associated lymphoid tissue lymphomas (MALT) are not anymore considered PTLDs [31]. It remains unclear whether other non-aggressive B-cell lymphomas, such as chronic lymphocytic leukaemia/small lymphocytic lymphoma, are still recognized as PTLD.

Treatment modalities and prognosis

There is no consensus about the optimal treatment of PTLD. Several therapeutic approaches are currently used; the limited number of treated patients, however, precludes a standardized therapeutic algorithm. It is generally agreed that three major strategies should be applied: restoration of the recipient's immunity (to limit the EBV infection), elimination EBV and removal of neoplastic B cells [12,51,52] (Figure 2).

Restoring the recipient's immunity

Reduction of immunosuppression. The evidence that immunosuppression of cytotoxic T lymphocytes enables proliferation of (EBV-transformed B) cells favours reduction of IS in patients with (EBV-related PTLD). IR or even withdrawal remains the first-line treatment [53]. The withdrawal or reduction of azathioprine, mycophenolate mofetil and CNI has been reported to be effective [53]; however, the clinical outcome is highly variable and depends on the type and lineage of PTLD (Table 2). Early lesions, especially in children, usually regress with IR [19]. The majority of M-PTLDs, however, do not respond to reduction of IS, and only about 50% of polymorphic PTLDs do. One of the factors predicting poor response to IR is the presence of *BCL6* gene mutations [54]. Association with EBV predicts a better outcome when compared with EBV-negative



Legend:
Aza – azathioprine; CNi – calcineurin inhibitor; CHOP – cyclophosphamide, doxorubicin, vincristine and prednisone; EBV – Epstein-Barr virus; St – steroids; MMF – mycophenolate mofetil; PSi – proliferation signal inhibitor

Fig. 2. Proposed treatment approaches in patients with PTLD.

Table 2. Efficacy of various PTLD treatment options after SOT

Response rate to treatment (%)					
Immunossupression reduction alone	Radiotherapy and/or surgery	CTL infusion	Chemotherapy	Rituximab	References
23–100[a]	Variable, depending on the location and the aggressiveness	48–100	24–65[b]	44–68	[19,45,55,57–62,66–78]

CTL, cytotoxic T lymphocytes.
[a]Depending on the type of PTLD and the association with EBV infection.
[b]Depending on the type of transplanted organ.

PTLD; however, subsets of EBV-negative PTLD patients have also been reported to regress with IR [55].

Adoptive immunotherapy. Because of the high mortality rate (ranging from 50% to 90%) when conventional IS reduction fails [56], better therapeutic approaches have been sought. One of the most promising strategies is adoptive immunotherapy with EBV-specific cytotoxic T lymphocytes (CTLs) [57]. The pathogenesis of PTLD provides a rationale for such an approach. In healthy people, virus-induced proliferation is kept under control by cell-mediated immunity elicited at the moment of primary infection. As immuno-compromised transplant recipients lack appropriate EBV-specific cell-mediated immunity, restoration can be obtained by administration of selected, ex vivo expanded, virus-specific T cells [57,58]. The requirement for generation of autologous lymphocytes results from the fact that more than 90% of PTLDs arising after SOT derive from recipient B cells. PTLDs usually arise from the donor B cells in bone marrow or haematopoietic stem cell recipients; therefore, donor lymphocyte infusions were applied in this latter population [59]. Unfortunately, in rapidly progressive forms of PTLD, the 2 or 3 months' time span required for generation of autologous CTL implies that allogeneic CTL in this setting is unrealistic.

Both auto- and allogeneic CTL administration have been shown to be safe, well-tolerated and effective methods of PTLD prophylaxis and treatment [60–62] (Table 2). Prophylactic use of CTL may be considered in a high-risk population, especially in EBV-negative heart or liver recipients who receive organs from EBV-positive donors. Although the results of the adoptive therapy are encourag-

Table 3. Efficacy of Rituximab in patients with PTLD after SOT

	Number of patients	Complete remission (%)	Partial remission	Overall survival (%/years)	Mean time of follow-up (months)
Rituximab					
Oertel [73]	17	52.9	5.9	56/3	24.2
Choquet [74]	43	44.2	16.2	67/1	12
Blaes [75]	11	54.5	9.1	54,5/1	10
Jain [76]	17	60	20	64/1 47/3 35/5	60
Milpied [77]	26	57.6	7.6	73/1	8
Rituximab alone or with chemotherapy					
Events [78]	59	73/3	40		

ing, only a limited number of centres applied this therapy. Several questions remain to be answered in relation to this approach, such as: the destination and survival of infused CTLs; migration to the target lesions or rather unspecific circulation; and influence of IS on these cells. For all these reasons, adoptive immunotherapy cannot yet be proposed as the first-line option in the majority of transplant recipients.

EBV elimination

Antiviral agents. Bearing in mind the pathophysiology of PTLD, it is unlikely that antivirals such as acyclovir or ganciclovir, even given in high doses, will be effective in the treatment of PTLD, particularly when used as a single agent. Because the EBV genome is incorporated into the infected B cell, these cells express a limited number of viral proteins that could be eliminated by these agents. Prophylaxis rather than treatment is currently indicated for high-risk patients (EBV+ donor and EBV− recipient pair), but the limited number and non-randomized character of related trials preclude definitive conclusions [63]. To date, it is believed that these agents can be useful in case of prevention of PTLD, particularly in EBV-seronegative patients and/or overimmunosuppressed recipients as well as in EBV-replicative forms of PTLD such as lymphoid hyperplasia [64].

Removal of the neoplastic B cells

Radiotherapy and surgery. Depending on the location and the aggressiveness of the lymphoid proliferation, surgery and radiotherapy may both be of value. These treatment modalities are recommended especially when PTLD is limited to a single lesion. Radiotherapy may be applied in patients with central nervous system involvement and in the rare cases of the extranodal natural killer/T-cell lymphomas, which represents the only form of T-cell-derived lymphoma in which radiotherapy as a primary treatment appears to yield favourable outcomes [65].

Prompt surgery of localized lesions, such as tonsillectomy or lung or liver resection (this means eventually retransplantation), combined with reduction of IS is critical for successful treatment of PTLD [45,66] (Table 2).

Chemotherapy. If there is no therapeutic response to reduction of IS, chemotherapy may be an option. Overall survival improves with multidrug regimens and is more effective than single-agent chemotherapy. The most frequently used combination includes cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). In a recent retrospective analysis with a median follow-up of 8.8 years, response rate to standard CHOP reached 65%; median overall and progression-free survival was 13.9 and 42 months, respectively [67]. Some forms of the disease, especially those derived from T cells, respond badly to chemotherapy [65].

When comparing various chemotherapeutic options, one should keep in mind that most reports concern small patient cohorts presenting with a heterogeneous spectrum of PTLD subtypes and of chemotherapy regimens [68,69]. Because chemotherapy is known, particularly in immuno-compromised patients, to be associated with significant toxicity and mortality, it should be reserved for disseminated forms of PTLD that are unresponsive to other types of treatment, especially in the era of availability of anti-CD20 antibodies.

Rituximab. Because the majority of PTLDs originate from B lymphocytes, monoclonal antibodies directed against B-cell surface antigens have become an interesting weapon in the treatment of PTLD. Rituximab® (Roche, Basel, Switzerland) is a mouse/human chimeric anti-CD20 IgG monoclonal antibody, consisting of human constant Fc regions linked to murine variable domains [70]. Murine Fab domains of rituximab bind the CD20 antigen, a transmembrane protein located on the surface of both malignant and normal, mature B lymphocytes. Its mechanisms of action include apoptosis and complement-mediated and antibody-dependent cell-mediated cytotoxicity of the targeted lymphocytes. The resulting activation of the effector cell ends up in cellular killing of lymphoma cells [71]. Rituximab has proven to be effective and safe in numerous retrospective and prospective studies on PTLD treatment, especially when combined with chemotherapy. However, one should take into consideration that the largest trials contain only from 11 to 59 patients (Table 3) [72–78].

Proliferation signal inhibitors. Despite the fact that sirolimus and everolimus were found to have antiproliferative potential in PTLD-derived cell lines in vitro as well as in solid tumours in a mouse in vivo model of PTLD, one must be careful when transposing these conclusions into the treatment of human PTLD [12,79]. Indeed, despite the po-

tential of PSI in the management of PTLD, the UNOS study unexpectedly reported a 2-fold increase in PTLD in RTRs treated with sirolimus after transplantation [13,80]. It is therefore difficult to draw definitive conclusions in relation to the use of PSI in the treatment of PTLD.

Summary

PTLD represents a serious problem after SOT. As the majority of risk factors cannot yet be influenced, prompt diagnosis and treatment are key objectives. Although the diagnostic and morphological criteria of different forms of PTLD are known, these objectives are not always reached. The 2008 WHO classification of PTLD was expected to refine the diagnosis and to increase its contribution to the treatment. Even though several changes were introduced in comparison to the former 2001 WHO classification, the judgment of the experienced pathologist still frequently allows to make a correct diagnosis. Does new classification mean better treatment? Sometimes yes, even small changes in classification may have an impact on therapy, especially in the era of modern drugs. Unfortunately, for the majority of PTLD patients, no significant impact on treatment options has arisen so far from these changes. Continuously, IS reduction remains the first-line therapy in the treatment of PTLD. As monomorphic or more aggressive forms of lymphoma do not respond well to IR alone, rituximab and/or multidrug chemotherapy should be added to the therapeutic algorithm of PTLD. In selected patients, IR along with the introduction of a PSI might be considered. High-risk populations may profit from preventive antiviral therapy. Further studies are necessary to establish the role of CTL infusion in cases of EBV-related PTLD. As the origin of PTLD is not exactly known, it is difficult to generate new treatments, and therefore large, randomized trials should be set up in order to further refine the therapeutic algorithm of PTLD in organ transplant recipients.

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