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Posttransplant Lymphoproliferative Disorders Following Kidney Transplantation

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1. Introduction

Posttransplant lymphoproliferative disorder (PTLD) is a rare but life threatening disorder following both solid organ and hematopoietic stem cell transplantation. The disorder is characterized by an uncontrolled proliferation of lymphocytes, caused by medication induced diminished immune surveillance. From a pathological point of view PTLD has a broad and heterogeneous spectrum of appearance, ranging from a benign condition to frank lymphoma. Although not required for diagnosis of PTLD, Epstein Barr virus (EBV) plays a major role in the pathogenesis of the majority of PTLDs. Currently the gold standard in diagnosis of PTLD remains biopsy with histopathologic examination to categorize every case according to the World Health Organization 2008 classification. Similar to its heterogeneous presentation treatment options are diverse and may include preventive, preemptive, curative and palliative approaches. However, the backbone of all PTLD therapies –except maybe for real palliation- should be (partial) reconstitution of the immune system.

2. Posttransplant malignancies

Historically long term follow up of solid organ recipients was limited by low graft and patient survival, mainly due to rejection and infectious complications. However, due to improvement in care and cure of these problems, as well as permitting increased donor and recipient age, posttransplant malignancies and cardiovascular disorders have emerged as the most important long term complications. The incidence of malignancies in solid organ transplant patients is estimated to be 20% following 10 year of chronic immunosuppression.[1] Skin cancer and lymphoproliferative disorders are the two most frequent malignancies in this specific patient population. Besides these two malignancies transplant patients are vulnerable to many other neoplasms.[2] These can occur *de novo,* can be a consequence of the underlying condition leading to transplantation or –in rare cases- can be transmitted by the donor.[3] Screening, early detection and staging have become an essential part of posttransplant management, given the good prognosis associated with *in situ* or low grade malignancies. Besides classical prevention including nicotine withdrawal and ultraviolet protection is essential.[1]

3. Incidence

The incidence of PTLD varies according to the type of organ transplanted. Compared to heart, lung and intestinal transplantation, incidence of PTLD in kidney transplant recipients is relatively low and is estimated to be 1-1.5%.[4] However, due to the high kidney transplant activities, the absolute number of PTLD is probably the highest in kidney transplant recipients. Lacking large prospective trials, retrospective single center studies and registry databases have been the major source of information in collecting epidemiology, incidence, (patient, disease and treatment related) characteristics and outcome data on PTLD. The main advantage of single center retrospective analyses is the provision of more detailed information (for example EBV status, specific information on immunosuppressive regimens,…), although the number of included patients is rather small. Transplant registries on the other hand provide information on a larger number of patients, but this information is mostly very limited and depends on the goodwill and the correct registration of the physicians and transplant coordinators. Information from large population based cohort studies indicate that standardized incidence ratios (SIR), reflecting the ratio between observed and expected cases, in solid organ recipients approach 10 in non Hodgkin lymphoma and 3.5 in Hodgkin lymphoma.[5,6] Initially the highest incidence was reported in the first year following transplantation ('early onset PTLD'), although currently 'late onset PTLD' is diagnosed more frequently, probably due to the improved survival of transplant patients and to increased awareness. Because of the above described limitations of registries incidence data are best derived from small single center series. However it seems that complete and standardized nationwide prospective data registry is mandatory to permit more precise estimates on incidence of PTLD in the transplant population.

4. Risk factors

Risk factors associated with occurrence of PTLD following SOT are multiple, as shown in table 1.

EBV status at time of transplantation (donor negative/recipient positive)
Type of transplanted organ
Intensity/duration of immunosuppressive therapy
Underlying disorder
Infectious agents other than EBV (CMV?, HCV?, ...)
Age of donor and recipient
Number and severity of rejection episodes
Cytokine gene polymorphisms
HLA alleles/haplotypes/mismatches/antibodies

Table 1. Risk factors for development of PTLD

4.1 EBV mismatch

The most important independent risk factor is pre-transplantation EBV mismatch (recipient seronegative/donor seropositive), leading to a 10-75 times greater incidence of PTLD compared to EBV seropositive recipients. As EBV seroconversion positively correlates with increasing age, the higher incidence of EBV mismatch in pediatric transplant procedures may explain the higher incidence of PTLD in childhood.[7] Although transplant patients with EBV mismatch are especially prone to occurrence of early PTLD[8], EBV seronegativity remains a risk factor after one year following transplantation.[9]

4.2 Type of organ transplantation

As already mentioned before, another major risk factor comprises the type of transplanted organ. Incidence of PTLD is highest in heart-lung and multivisceral transplantation (up to 20%), followed by liver (4.5%), heart and lung (2.5%), pancreas (2%), kidney (1-1.5%) and finally matched related and unrelated hematopoietic stem cell transplantation (0.5-1%).[4] In a retrospective analysis of the Collaborative Transplant Study (CTS) database relative risk (RR) was highest in heart-lung transplantation (RR 239.5) and lowest in kidney transplant recipients (RR 12.6).[10] The reason for these differences are largely unknown. Possible hypotheses include the fact that high risk transplantations require more profound immunosuppression and contain large amounts of lymphoid tissue, leading to increased risk for EBV infection.[4]

4.3 Immunosuppressive regimen

A third important risk factor is the use of potent and prolonged immunosuppressive medication used to prevent or treat graft rejection. Taken together the risk for developing PTLD seems to be correlated with the cumulative intensity of immune suppression, leading to decreased viral and malignant surveillance. In this way repeated episodes of acute rejection increase the risk of PTLD.[2] However, measuring the cumulative immunosuppressive intensity is not easy. Firstly, transplant protocols almost always use combination therapy, making the determination of each drug separately very difficult. Secondly, registration of dose modifications/interruptions during the posttransplant period requires a major effort and consequently registration of these activities is very poor. Thirdly, besides maintenance therapy induction and repeated episodes of anti-rejection therapies might influence the risk of PTLD. Finally, no single laboratory test exists measuring the total amount of immunosuppression in a patient.[11] Due to these difficulties in determining the overall role of immunosuppression, interest has largely shifted to identification of the role of specific immunosuppressive medication.

4.3.1 Calcineurin inhibitors

Currently data on a possibly increased risk of calcineurin inhibitors (CNI) are very controversial. Although structurally unrelated to cyclosporine A, tacrolimus' mechanism of action is similar with inhibition of calcineurin and subsequent of Interleukin 2-production being the common pathway.[12] However, the immunosuppressive activity of tacrolimus seems to be stronger compared with cyclosporine A, leading to improved kidney graft survival and prevention of rejection at 1 year.[13] These stronger immunosuppressive properties seem to be translated in a higher risk for development of PTLD. In their CTS

database Opelz et al found a statistical significant increased cumulative incidence of PTLD in patients receiving combination therapy with tacrolimus and mycophenolate mofetil (MMF) or azathioprine compared with patients on cyclosporin A and MMF or azathioprine.[10] This increased risk of tacrolimus compared to cyclosporin A was confirmed in a United States cohort of kidney recipients, but only in case no induction therapy was given[14], and in a Organ Procurement and Transplant Network/United Network for Organ Sharing (OPTN/UNOS) registry study, though the difference didn't reach statistical significance in this last trial.[15] On the other hand Pirsch et al didn't find a difference in PTLD incidence in a prospective randomized study comparing both CNI following kidney transplantation. However, as the follow up in this study was only one year no real conclusions can be made.[16] An important characteristic of CNI is their ability to enhance production of transforming growth factor β1 (TGFβ-1). Together with the finding that cyclosporin A can cause impaired DNA repair, a direct oncogenic effect might contribute to the occurrence of malignancies in patients treated with CNI.[17-19]

4.3.2 Antimetabolites

Azathioprine is a purine analogue which is, following metabolisation and conversion to different compounds, incorporated into replicating DNA.[20] In prevention of renal graft rejection it is largely replaced by MMF, which has been proven to be more effective than azathioprine in the prevention of allograft rejection.[21] MMF is converted in the liver to its active compound mycophenolic acid, which blocks inosine monophosphate dehydrogenase, disturbing DNA synthesis.[20] Azathioprine has well known synergism with ultraviolet radiation in carcinogenesis, leading to increased risk of skin cancers.[22] Besides the drug also induces mutagenesis due to DNA mismatch repair deficiencies, explaining also the observed increase of therapy related acute myeloid leukemia/myelodysplastic syndrome.[23] In contrast to azathioprine, several studies have shown that MMF is not associated with an increased risk[24,25] and even with a reduction in the number of PTLDs following kidney transplantation.[14,26] However, in the CTS report incidence of PTLD was similar irrespective of the use of azathioprine *versus* MMF.[10] As already discussed above combination with tacrolimus was associated with an increased risk compared to combination with cyclosporin A.[10]

4.3.3 Mammalian target of rapamycin inhibitors

Mammalian target of rapamycin (mTOR) inhibitors display their activity by blocking the serine-threonine kinase mTOR.[27] Currently two of these proliferation signaling inhibitors (PSI) are used in organ transplantation, namely sirolimus and everolimus. Apart from its immunosuppressive properties, mTOR inhibitors also possess antiproliferative characteristics, making their use very attractive especially in high risk patients and in CNI-free regimens.[28-30] However, in a recent retrospective study in kidney transplant patients maintenance therapy was associated with higher PTLD incidence.[31] In addition Mathew et al performed a multicenter analysis of renal transplant patients receiving sirolimus as base therapy or as maintenance. Although the two-year incidence of malignancies, especially skin cancer, was significantly lower, the risk of developing PTLD was increased in comparison with classical immunosuppressive therapy, especially when high dose sirolimus (5 mg/day) was given.[32]

4.3.4 Polyclonal T cell depleting antibodies

Initially used in the treatment of acute rejection following organ transplantation and of graft-versus-host disease after bone marrow transplantation, the use of anti-lymphocyte and anti-thymocyte globulins (ALG/ATG) has shifted to the prevention of both severe complications of transplantation. These antibodies bind to different antigens, not only on T cells but also on most other immunological players, although exact mechanism of action has not been fully understood yet.[33] The use of ATG was found to increase the risk for PTLD in hematopoietic stem cell transplantation[34], however its role in solid organ transplantation is less well established. In most registry studies there is a clear association between the use of ATG and the occurrence of PTLD.[10,14,31] On the other hand Hardinger et al recently published the results of a small but prospective, randomized, double-blind study in kidney transplant recipients comparing induction therapy with rabbitATG (Thymoglobulin) and horseATG (ATGAM). With 10 years follow up the composite primary endpoint of freedom from death, graft loss or acute rejection was significant higher in the Thymoglobulin-group. Importantly no patients in the Thymoglobulin group (n=48) and two in the ATGAM group (n=24) were diagnosed with PTLD.[35] In another registry study Dharnidharka et al found an increased risk in kidney transplant recipients treated with horseATG, but not with rabbitATG, although the follow up in the latter group was significantly shorter.[36]

4.3.5 Monoclonal T cell depleting and non-depleting antibodies

Muromonab CD3 (= OKT3) is a murine monoclonal antibody directed against the CD3 antigen on the surface of human T cells.[37] In their CTS study Opelz et al reported a higher incidence of early PTLD in patients receiving induction therapy with OKT3 or ATG.[10] However, other studies failed to show an association between OKT3 induction and PTLD.[37] Mainly due to xenosensitisation, pulmonary toxicity and to its relationship with malignancies, its use has been largely replaced by polyclonal or other monoclonal depleting/non-depleting antibodies.

Alemtuzumab is a humanized rat monoclonal antibody directed against the CD52 antigen. This antigen is expressed on the surface of peripheral blood lymphocytes, natural killer cells, monocytes and macrophages.[38] Because of the depletion of both B- and T-cells alemtuzumab possesses a theoretical advantage of reduced B cell mass and hence protection against (EBV related) B cell proliferation. Although data on the association between alemtuzumab induction and PTLD in kidney transplant recipients are limited, there seems to be no association.[39,40] This was confirmed in a UNOS registry study comparing no induction, depleting and non-depleting induction therapy.[31]

Based on decreased acute rejection rates anti-interleukin-2 receptor (CD25) monoclonal antibodies have emerged as an important part of immunosuppressive regimens in kidney transplant recipients due to selective depletion of activated T cells. Basiliximab is a chimeric antibody, whereas daclizumab is humanized.[41] In a study using data from the Scientific Registry of Transplant Recipients Bustami et al found a significant increased adjusted relative risk for PTLD using basiliximab or daclizumab.[42] However, other registry studies failed to find an association between anti-CD25 induction therapy and risk for PTLD, leading to the general assumption that basiliximab and daclizumab do not increase the risk for PTLD.[10] Magliocca et al retrospectively compared induction therapy with alemtuzumab and basiliximab in combined pancreas-kidney transplantation, but found no difference of PTLD occurrence in the first two years following transplantation.[43]

4.3.6 Co-stimulation blockade.

For their activation, T cells require two signals. Signal 1 represents interaction between the T cell receptor (TCR) and major histocompatibility (MHC) complex on an antigen presenting cell (APC). Co-stimulation signaling (signal 2), also achieved by interactions between APCs and T-cells, is obligatory for complete activation of the T cell. In the absence of this signal, T cells will fail to proliferate and will finally become apoptotic or anergic. Of these signal 2 interactions, those between B7 (CD80 and CD86) and CD40 [APC] and CD28 and CD40L (CD154) [T cells] respectively seem to be the most important for T cell activation. After CD28 has delivered a signal for T cell activation, CTLA4 (cytotoxic T-lymphocyte-associated antigen 4) is transiently upregulated on T cells. This molecule is a negative regulator of T-cell activation by inhibiting binding of CD28 to CD80 and CD86, due to its higher affinity compared with CD28.[44]

Inhibiting of this co-stimulation signal has become a promising approach in both autoimmune disorders and transplantation, leading to two phase III trials (BENEFIT and BENEFIT-EXTENT) comparing the selective co-stimulation blocker belatacept and cyclosporin A in kidney transplant recipients. Belatacept is a human fusion protein combining the extracellulair domain of CTLA4 with the constant-region fragment (Fc) of human IgG1. In both trials patients treated with betalacept-containing immunosuppression had an increased incidence of PTLD. Interestingly, in the BENEFIT-EXTENT study 4 of 5 PTLD cases showed central nervous system involvement. Risk factors for PTLD included EBV seronegativity pre-transplantation and the use of a more intensive regimen of belatacept.[45,46] The former finding has led to the recommendation to abandon the use of belatacept in patients with a seronegative EBV status before transplantation.[47] In another phase I/II trial with efalizumab, targeting CD11a, the alpha subunit of lymphocyte function-associated antigen-1 (LFA-1), 3 out of 38 kidney transplant recipients receiving combination therapy with high doses efalizumab and cyclosporine A were diagnosed with PTLD.[48]

In summary we can conclude that currently no firm conclusion can be made for individual contribution of these different drug classes with respect to the risk for PTLD, although use of monoclonal anti-CD3, polyclonal anti-thymocyte antibodies (ATG) and possibly some new and potent agents seem to be associated with an increased risk in most studies, whereas mycophenolate mofetil, monoclonal anti-CD52 and anti-IL2-R-antagonists probably are not. However, taking into account the increasing number of late onset PTLD, cumulative intensity seems to influence the risk mostly.

4.4 Other risk factors

Many other risk factors have been described and proposed. However their exact relationship with development of PTLD is less established in comparison to the above discussed factors.

Although the role of patient related risk factors including age, gender and race have been described, literature results are too conflicting to draw any conclusion at this moment.

Underlying immunodeficiency disorders, especially primary immune deficiency (PID) and autoimmune hepatitis leading to hematopoietic stem cell and liver transplantation respectively, seem to be associated with increased risk for development of PTLD.[49,50] The main reason for this probably is the prolonged (disease or treatment related) pre-

transplantation immune compromised situation. In renal transplantation no such association has been found. Whether end stage renal disease (ESRD) and subsequent need for renal replacement therapy (RRT) contribute to the PTLD risk following kidney transplantation was investigated in a large population based Australian cohort study, comparing cancer SIRs for patients with ESRD before RRT, patients on RRT and transplant patients. Because SIRs for most cancers, in particular lymphoproliferative disorders, were not increased in the ESRD and RRT groups, the risk of PTLD seems to be associated mainly by the iatrogenic immunosuppression posttransplant.[5]

About 80-85% of the PTLD cases are associated with EBV primary infection or reactivation (described in 'Pathogenesis').[4] The pathogenesis of the remaining 15-20% is less clear. These EBV negative cases have the tendency to occur late following transplantation. Possible explanations include involvement of other infectious agents or loss of EBV during PTLD evolution ('hit and run' hypothesis).[51] This hypothesis is supported by the description of Burkitt and Hodgkin lymphoma cases who seem to lack expression of EBV genes, but still have fragments of EBV DNA.[52] Different viruses have been identified as important contributors of lymphomagenesis, both in immunocompetent and immunosuppressed patients. Although Hezode et al reported on a possible higher incidence of PTLD in liver transplant patients with underlying hepatitis C cirrhosis[53], this finding could not be confirmed in a recently published large cohort study in solid organ transplant recipients.[54] Cytomegalovirus (CMV) is another virus which has been suggested as potentially PTLD-inducing virus in some single center studies, yet the number of cases are very small and currently there is no hard evidence to support its role in PTLD.[55-57]

Despite different cohorts of patients receive a similar cumulative intensity of immunosuppression, only a minority of patients will develop PTLD, pointing to a possible role of genetic susceptibility. In this way different authors have shown an increased risk for PTLD associated with cytokine gene and cytokine receptor gene polymorphisms including Tumor Necrosis Factor-α, Interferon-γ, Interleukin-10 and Transforming Growth Factor-β.[58-60] Although the use of these molecular techniques currently is not applicable in daily practice, they might become useful in predicting the risk for PTLD. However, recent data on some previously described predictive cytokine receptor gene polymorphisms were not able to confirm these findings.[61]

Given the important role of the Human Leucocyte Antigen (HLA)-system in transplantation immunology, its predictive role in development of PTLD has been suggested. Most evidence has derived from small patient populations with isolated, but not confirmed findings supporting the contribution of specific donor/patient HLA alleles, HLA haplotypes, HLA mismatches and pre-existing HLA-antibodies in the development of PTLD in transplant recipients.[62-64] Clearly, larger studies are needed to further clarify this complex association.

5. Pathogenesis

The pathogenesis and biology of PTLD is complex and multifactorial, as reflected by the large heterogeneity in time of occurrence and clinical and pathological presentation. In the majority (80-85%) of cases onset of PTLD is Epstein Barr virus (EBV) driven, leading to uncontrolled B-cell proliferation due to deficient cellular immune response. EBV is a herpesvirus, infecting more than 90% of the world population worldwide. Following primary infection, the virus persists in the host during the whole life mostly without harmful effects. However, EBV has

the capacity to transform B cells, resulting in different lymphoproliferative disorders, in particular Burkitt non Hodgkin lymphoma, Hodgkin lymphoma and PTLD.[65]
The pattern of different viral gene expression used by EBV is called the growth program. These genes encode for different functional homologues of B-cell factors involved in cell cycle regulation, inhibition of apoptosis and signal transduction.[65] In this way EBV is able to use the normal B cell program and promote proliferation and transformation of these cells.[66] In healthy persons EBV is kept in a silent state in memory B cells without expressing any viral protein, corresponding with latency program (type 0). Based on the gene expression of different EBV-encoded genes, other growth programs can be seen (table 2). In Burkitt lymphoma the majority of EBV positive cases show a highly restricted latency I program of infection (Epstein Barr nuclear antigen-1 = EBNA-1 only program), whereas EBV positive Hodgkin lymphoma is characterized by a type II latency (default) program. Lymphoproliferative disorders occurring in immunosuppressed patients (PTLD and some HIV related lymphomas) most often express the latency III (growth) program, although other gene expression patterns have been described in PTLD.[65,67] Latency III program is critical for B cell activation and transformation, which becomes uncontrolled if not inhibited by cytotoxic T cell activity.[68] This explains why reduction of immune suppression, leading to (partial) restoration of immune control, is considered the first and most important therapeutic intervention, especially in early (EBV positive) PTLD cases.

Transcription program	EBV genes expressed	Occurrence
Type 0 (latency)	None	Peripheral blood memory B cells (healthy persons)
Type I (EBNA-1 only)	EBNA-1	Burkitt NHL
Type II (default)	EBNA-1, LMP-1, LMP-2A	Hodgkin lymphoma
Type III (growth)	EBNA-1 till -6, LMP-1, LMP-2A, LMP-2B	PTLD

Table 2. EBV transcription programs in human lymphoproliferative disorders

Another important mechanism in the pathogenesis of PTLD is situated at the graft organ level. Chronic antigen stimulation of recipient B cells by donor antigens may give rise to B cell proliferation and PTLD in case of inadequate immune surveillance. On the other hand, donor lymphoid cells (especially in organ transplantation with a high lymphoid load such as lung, bowel and liver transplantation) may be exposed to chronic recipient derived antigen stimulation, leading to donor lymphoid cell proliferation in a tolerant environment.[69] These cases of donor derived PTLD are characterized by early presentation and are often limited to the allograft, in contrast to the more frequent recipient derived PTLD occurring later and disseminated at presentation.[70]

6. Symptoms

The clinical presentation of patients with PTLD is very variable, ranging from an asymptomatic finding to fulminant general deterioration rapidly evolving into multi organ

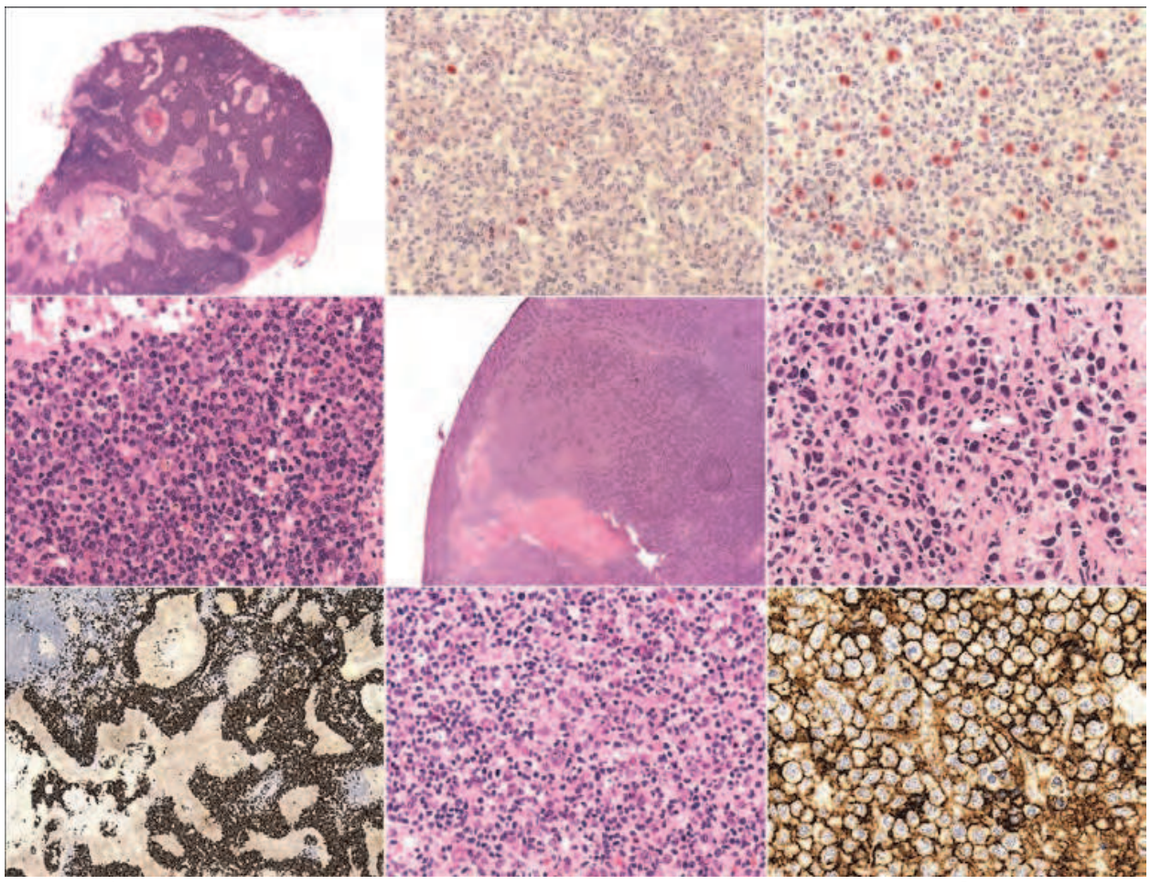
failure. Differential diagnosis with graft rejection (in case of graft involvement) and infectious complications/sepsis (in case of symptomatic disseminated disease) may be very difficult. Children may present with painful throat, fever and adenopathies resembling an infectious mononucleosis-like picture with tonsilla and Waldeyer ring involvement. Besides classical nodal involvement with or without B symptoms, PTLD is characterized by a high incidence of extranodal invasion, including bone marrow and central nervous system (CNS) involvement.[71] Although initially a high incidence (15%) of primary and secondary CNS lymphoma was described in PTLD patients[72], recent reports show incidences between 5 and 13%.[73-75]
As already discussed above early PTLD may have a different presentation compared to late PTLD with more frequently positive EBV state and involvement of the allograft.[70,76,77]

7. Diagnosis

The gold standard in diagnosis of PTLD remains biopsy with histopathologic examination, although cytological preparations may also be useful, especially in case of effusion lymphoma. According to the current World Health Organization (WHO) PTLD is a subtype of 'Immunodeficiency associated lymphoproliferative disorders', in close correlation with other Primary Immune Deficiency (PID), Human Immunodeficiency Virus (HIV) and Methotrexate-associated lymphoproliferative disorders.[78]
In addition to morphological examination of the biopsy immunohistochemical analysis with at least CD3 and CD20 staining to differentiate between B cell and T cell origin is necessary in the evaluation of suspected PTLD. Other markers, including CD15, CD30, CD38, CD138 and MUM1 may provide additional information in case of rare subtypes. Cytogenetic and molecular analysis may provide important information on the monoclonal nature of the disorder and may help in understanding the biology of PTLD by analyzing oncogenes and tumor suppressor genes. Finally presence or absence of EBV should be demonstrated in all cases, which can be done by different techniques. EBV Early RNA (EBER) *in situ* hybridization is the preferred method as EBER transcripts are abundantly present, show relative stability and are expressed in all types of latency. Alternatives include immunoperoxidase staining for EBV Latent Membrane Protein 1 (LMP-1) or the use of Epstein Barr nuclear antigen-2 (EBNA-2) antibodies. However, LMP-1 and EBNA-2 are not expressed in all latency types, leading to false negative results.[79]
Based on morphological and immunohistochemical findings the WHO distinguishes four major categories of PTLD, ranging from polyclonal early lesions to aggressive monoclonal lymphoproliferative disorders resembling the broad spectrum of typical lymphomas occurring in immunocompetent persons (figure 1).[78]

7.1 Early lesions

Two typical early lesions have been recognized by the WHO: plasmacytic hyperplasia and infectious mononucleosis-like lesions. These abnormalities are characterized by a preservation of the underlying architecture of the tissue involved. They typically occur early (within one year) following transplantation and the large immunoblasts are infected with EBV, as shown by EBV Early RNA (EBER) *in situ hybridization* or EBV Latent Membrane Protein (LMP)-1 staining. These lesions are considered the first morphological changes in PTLD and their benign characteristics have been confirmed by the absence of oncogene or tumor suppressor gene mutations.



A B C
D E F
G H I

A-D. Early lesion, plasmacytic hyperplasia. A. H&E low power view. Preserved lymph node architecture. B. High power view shows numerous plasma cells. C. Plasma cells stain with CD138/syndecan. D. EBER *in situ* hybridisation shows small amount of positive cells.
E-G. Polymorphic PTLD. E. Low power view shows disturbed lymph node architecture. F. Higher power shows a polymorphic infiltrate composed of plasma cells, lymphocytes (small, medium-sized, large and Reed-Sternberg-like). G. EBER ISH shows numerous positive cells.
H-I. Monomorphic PTLD. H. Diffuse proliferation of large atypical cells. I. CD20 staining shows their B-cell origin (Courtesy to Prof Thomas Tousseyn).

Fig. 1. Morphology and immunohistochemistry of PTLD

7.2 Polymorphic PTLD

This subtype is characterized by a mixed lymphoproliferation consisting of a large spectrum of different cells like immunoblasts, mature plasma cells and intermediate sized lymphoid cells. Different specific features including atypia, necrosis and mitotic figures may be seen in the biopsy. Immunophenotyping, which has no real value in early lesions, shows a variable mixture of both B and T cells. In most cases this subtype is EBV related as well. In contrast to early lesions clonal abnormalities may be present, reflecting the transition to malignant transformation.

7.3 Monomorphic PTLD

This subtype is characterized by architectural and cytological abnormalities which can impossibly be distinguished from lymphomas occurring in immunocompetent patients. Similar to classical lymphoproliferative disorders they can be subclassified in B-, T- and NK-cell non Hodgkin lymphoma (NHL). Although not always present, most of the monomorphic PTLDs seem to be EBV driven as well. Besides the clear monoclonal appearance, additional mutations in oncogenes (N-Ras, c-Myc,…) and tumor suppressor genes (p53,…) are not uncommon.

In the majority of cases monomorphic PTLD has a B-cell phenotype, with diffuse large B cell lymphoma (DLBCL) being the prototype. Although immunoblastic, centroblastic and anaplastic DLBCL have been described, the clinical significance of these morphological subtypes is not entirely clear. However, being CD20 negative, anaplastic DLBCL may confer a poor prognosis given the fact that anti-CD20 therapy cannot be used. Other types of B-PTLD include Burkitt(-like) NHL, plasmablastic NHL and plasma cell myeloma, which can be EBV driven as well.

In contrast to B-PTLD T/NK lymphomas are rather rare following transplantation. Most T cell cases do not show positive EBV staining, although EBV positive cases have been described. Possible explanations for this last finding include expression of CD21 or other not yet identified receptors leading to EBV infection. The largest series of T- and NK-PTLD, including 130 cases, has been described by Swerdlow et al with 69% occurring after kidney transplantation. Different subtypes were identified including peripheral T cell lymphoma, unspecified (PTCL,U), hepatosplenic gamma-delta T cell lymphoma (HSGDTCL) and anaplastic large T cell lymphoma (ALCL). Most cases occurred late following transplantation and only 37% of the cases were EBV positive. The prognosis was very poor with overall survival of only 6 months, although EBV positive cases tended to have a better outcome.[80]

7.4 Hodgkin lymphoma / Hodgkin-like lymphoma

Although this subcategory constitutes only a very small proportion of PTLD, population based cohort studies have shown SIRs of 3.5 for Hodgkin lymphoma following solid organ transplantation[5,6], with the risk being even higher after bone marrow transplantation.[81] Despite most evidence is based on case reports and smaller case series HL-PTLD is mostly EBV related and is associated with a better prognosis compared to other subtypes of PTLD.[82,83]

Whether there is a difference between monomorphic Hodgkin lymphoma (HL) and polymorphic Hodgkin-like lymphoma (HLL) following transplantation is not entirely clear. In an overview of the literature on this topic Semakula et al described different clinical, immunophenotypic and molecular features of both subtypes, with HLL behaving more aggressively and probably requiring a NHL-therapeutic approach, whereas real HL may be treated in the same way as classical HL.[84]

Although the WHO 2008 classification provides an important framework in correct diagnosis, some problems remain. Firstly, apart from these four categories other lymphoma subtypes have been reported following transplantation, though these have not been included in the current WHO classification. Aull et al described 16 cases of marginal zone lymphoma following solid organ transplantation. The majority of these lymphomas showed gastric localization, occurred late and were associated with Helicobacter pylori positivity (and not EBV). Treatment of most cases included reduction of immunosuppression and helicobacter pylori eradication therapy, leading to excellent disease control and prognosis.[85] It can be expected that, due to improved survival and to increasing age of transplant recipients, more

indolent lymphoproliferative disorders will occur in the transplant population. Whether these lymphomas should be considered real PTLD or only reflect an ageing population needs to be explored further.[86] Secondly it's important to stress that progression or recurrence of a lymphoproliferative disorder already existing before transplantation, does not fulfill criteria for PTLD.[87] Finally, it's clear that not all cases are easily classified in the well known lymphoma categories, reflected by the finding of several "grey zone lymphomas".

8. Staging

Once the diagnosis of PTLD has been established staging examinations need to be performed in order to exactly define the extent of involvement of lymph nodes and organs, including the allograft itself. Staging tools are comparable to those used in classical lymphomas with computed tomography (CT) scan, magnetic resonance imaging (MRI) of the brain and bone marrow examination being of great importance. The staging system most used in lymphoma is the Ann Arbor Classification (table 3).[88] However, as extranodal involvement is a frequent feature of PTLD and because CT is not able to discriminate between vital and non-vital tumor lesions, CT scan may not be the most appropriate staging tool. Besides, the use of intravenous contrast may be relatively contra-indicated in kidney transplant recipients with compromised renal function. These drawbacks have lead to emerging interest in the use of ^{18}fluorodexyglucose- positron emission tomography (FDG-PET) scan. FDG-PET is a functional imaging technique which allows characterization of metabolic active tissues by demonstration of elevated FDG-uptake in these tissues (figure 2). Last decade the use of FDG-PET has shown impressive results in detection and staging of several lymphoma subtypes, especially aggressive lymphomas. Besides FDG-PET can be used for response evaluation and follow up. However, as PET scan lacks anatomic detail due to its poor resolution, a combined approach of PET and CT has been developed for both staging and response assessment purposes. Till now, experience with PET with or without CT imaging in PTLD has been limited to rather small retrospective single center experiences. Taken together these reports reveal that PET scan may have a high sensitivity for the detection of PTLD lesions, although PET scan has shown a low accuracy in low grade lymphomas and is not the preferred examination in case of suspicion of central nervous system (CNS) localization. In the latter situation MRI of the brain and cytological examination of cerebrospinal fluid should be performed.

Stage I	**Involvement of a single lymph node region (I) or one extralymphatic site (IE).**
Stage II	Involvement of two or more lymph node regions, at the same side of the diaphragm (II) or local extralymphatic extension plus one or more lymph node regions at the same side of the diaphragm (IIE).
Stage III	Involvement of lymph node regions on both sides of diaphragm (III) which may include the spleen (IIIS) or accompanied by local extralymphatic extension (III_E) or both (IIIES).
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs or sites, with or without associated lymphatic involvement.

Each stage number is followed by either **A** (absence of B-symptoms) or **B** (presence of B-symptoms: unexplained weight loss > 10% baseline during 6 months before, unexplained fever > 38°C, night sweats).

Table 3. Ann Arbor staging system for lymphoproliferative disorders

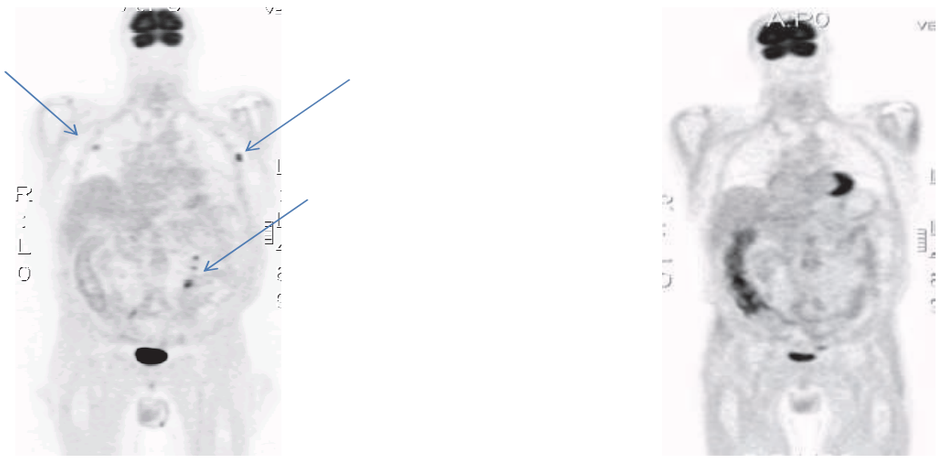


Fig. 2. Role of PET scan in staging and follow up

A. Heart transplant recipient diagnosed with PTLD subtype DLBCL. Pet scan shows lymphoma localisation left axilla, lung bilateral and small intestine. This scan illustrates the increased incidence of organ involvement in PTLD compared to findings in lymphoma in immunocompetent patients. B. PET scan shows a complete metabolic remission following reduction of immunosuppression and four administrations of rituximab (Courtesy to Dr Lieselot Brepoels).

9. Prevention

The often very aggressive presentation and the poor prognosis of PTLD has led to an increased interest in adequate prevention of the disorder. At this moment many centers, similar to the intensive viral monitoring following allogeneic stem cell transplantation, advocate the use of EBV viral load monitoring as a tool to initiate pre-emptive therapy in case of rapid increase of the viral load. Classical EBV serology (anti-Viral Capsid Antigen [VCA] IgM and IgG, EBV-EA and EBNA) is not reliable in patients with a dysfunctional immune system, in particular transplant recipients.[89] In this patient population viral load measurement by quantitative polymerase chain reaction (PCR) is a much more reliable test. During the last decades many authors have reported their experience with serial EBV viral load monitoring, both in adult and pediatric solid organ transplant recipients (as reviewed in ref 90 and 91).[90,91] Although these series confirm the utility of serial monitoring in prevention of PTLD, the results need to be analyzed with caution.

Firstly, most results are derived from retrospective single center studies, often mixing different populations.

Secondly, there is a huge heterogeneity in methods, cut off values and source of samples (whole blood *versus* plasma *versus* peripheral blood mononuclear cells). In a prospective single center study Tsai *et al* compared PCRs with different gene targets (EBNA, EBER and LMP) and different sample sources (plasma and lymphocytes) in lung transplant patients. Free plasma EBNA PCR showed the highest specificity and positive predictive value,

making this test useful in identification and monitoring of patients with EBV-related PTLD. However, the whole PCR panel was needed to rule out the presence of EBV-related PTLD.[92] Finally, pre-emptive decisions are very variable between different centers, ranging from more intensive monitoring to reduction of immunosuppression and antiviral therapy to monoclonal anti-CD20 therapy.

In order to improve positive predictive value of EBV viremia, some authors propose to combine EBV PCR with measurements of T cell immunity like absolute lymphocyte count (<300/mm³) or the absence of EBV-specific CD8-positive cytotoxic T cells. However, these combinations have not been validated in larger series yet.[93,94] Another approach may be the combination of EBV viral load and use of cytokine polymorphisms, as shown in a study in pediatric liver transplant recipients.[95]

In addition other, but less used, preventive tools include incorporation of cytokine measurements. Elevated Interleukin-6 (IL-6) levels have been associated with the occurrence of PTLD following solid organ transplantation, whereas a strong correlation has been found between IL-10 and EBV viral load.[96,97]

10. Treatment

As development of PTLD is the consequence of an imbalance between immunosuppression and immunosurveillance, different approaches can be made in the treatment of the disorder. These approaches include improving reconstitution of the immune system, targeting the uncontrolled proliferation of malignant B cells and decreasing (EBV) viral load.[98] Unfortunately treatment for PTLD is largely based on retrospective data with only few prospective and no randomized trials being performed till now. As a consequence formal recommendations are lacking and currently treatment is largely physician or transplant center dependent.

Taking into account that PTLD is always associated with a high degree of overimmunosuppression, the most important therapeutic intervention seems to be reduction of immunosuppression, leading to (partial) cellular (EBV specific) immunity reconstitution. However, in many cases this is insufficient and further therapy is needed. The spectrum of therapeutic options, including antiviral therapy, cytokines and chemotherapy, recently has been expanded with the use of monoclonal anti-B cell antibodies and EBV specific immunotherapy. In this chapter we will review the different currently used and future therapeutic options.

10.1 Restoration of the immune system

10.1.1 Reduction of immunosuppression

Reduction of immunosuppression (RIS) has been considered standard therapy in PTLD following kidney (and other types) transplantation allowing reconstitution of the immune system, in particular EBV-specific cytotoxic lymphocyte response.[99] Although no consensus has been reached, most transplant physicians agree to stop antimetabolites, reduce the calcineurin inhibitor dose with 50% and continue treatment with steroids.[100] It seems appropriate to re-evaluate two to four weeks following initiation of RIS, if the clinical situation doesn't oblige urgent treatment. Response rates to RIS alone in PTLD have a very wide variation ranging from almost no response to response rates exceeding 50%. This heterogeneity reflects the lack of standardization with respect to duration of RIS before re-evaluation, response criteria and reduction regimen. Reshef et al recently published their

experience with RIS alone in 67 solid organ transplant recipients diagnosed with PTLD. Overall response rate was 45%, including 37% complete responses. The authors conclude that RIS alone might be a useful therapy in low risk PTLD patients as the presence of bulky disease (> 7cm), advanced stage (Ann Arbor III-IV) and higher age (> 50 year) were independently associated with lack of response to RIS.[101] In a recent prospective trial however, examining the use of sequential RIS, interferon-α-2B and chemotherapy in 16 PTLD patients following SOT, RIS was associated with an overall response rate of 6% without any complete remission, even though acute graft rejection was seen in one third of the patients. Half of the patients showed progressive disease during the period of RIS.[102]
The main problem associated with RIS is rejection of the allograft. In contrast to heart- and lung transplantation kidney recipients can still be rescued by hemodialysis, explaining the tendency for more aggressive RIS in kidney transplantation compared to other types of organ transplantation. Whether immunosuppressive therapy can be safely reduced during chemotherapy was recently addressed in a retrospective analysis of 58 kidney transplant recipients. A significant improvement in renal function was observed in patients treated with RIS followed by CHOP chemotherapy with or without rituximab, reflecting the immunosuppressive properties of chemotherapy.[103] However, the question whether immunosuppression can be disrupted completely during chemotherapy remains unanswered. Even if immunosuppression is discontinued during chemotherapy, a reduced dose is re-initiated after termination of the chemotherapy in most centers.
Proliferation signaling inhibitors (PSI) or mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus) possess a unique combination of both immunosuppressive and anti-proliferative properties. From a theoretical point of view they may show superiority in the treatment of malignancies in transplant recipients, which was confirmed in small single center trials.[28,104] However, as stated before, maintenance therapy with PSI might be associated with increased risk for PTLD.[31,32]

10.1.2 Adoptive immunotherapy

The use of EBV specific cytotoxic lymphocytes (CTLs) is another attractive option to induce EBV specific cellular immune response.[65,68] This type of adoptive immunotherapy was first described in the early 1990s in patients with EBV related PTLD following hematopoietic stem cell transplantation. In contrast to PTLD following SOT, in which the disorder mostly arises in recipient lymphocytes, hematopoietic stem cell related PTLD mostly derives from donor cells. In this way donor lymphocyte infusions were given to evoke an EBV-specific response. Despite impressive response rates, a high incidence of graft versus host disease was observed.[105,106] Due to this strong alloreactive mediated complications, further attempts were made to isolate expanded EBV-specific CTLs. By infusing these CTLs, both autologous (recipient derived PTLD) and allogeneic (isolated from the donor itself or from a bank of partial HLA-matched voluntary donors), promising results were obtained in PTLD patients after SOT, recently reviewed by Merlo *et al*.[107] However, wide applicability has been limited so far because of pronounced labor-intensive procedure and by availability problems.

10.1.3 Cytokine therapy

Interferon-alpha (IFN-α) is a cytokine with well known anti-viral and anti-neoplastic properties.[108] In the late 90s several case reports and small case series have been published showing effectiveness of cytokine therapy in the treatment of PTLD. Davis *et al* treated 16 newly diagnosed patients with subcutaneous IFN-α, leading to a complete response rate of

50%. However treatment was associated with a high rate of graft rejection and was poorly tolerated.[109] However, in their recent report on the use of sequential RIS, IFN-α-2B and chemotherapy in PTLD Swinnen *et al* observed a lower overall response rate of 30% with only 15% patients with complete remission.[102]

10.2 Anti- B cell therapy

10.2.1 Cytokine therapy

Interleukin-6 (IL-6) is a cytokine produced by monocytes, fibroblasts and endothelial cells, promoting the growth of EBV-immortalized cells *in vitro*. In the early 90s Tosato *et al* demonstrated elevated serum IL-6 levels in patients with PTLD, pointing to a possible role in the pathogenesis of the disorder and providing an opportunity for new therapeutic modalities.[110] In a multicentric phase I-II trial assessing the role of anti-IL-6 monoclonal antibodies in non-responders to RIS 8 out of 12 patients responded without major side effects.[111] Although cytokine therapy clearly showed promising results in the treatment of PTLD, currently its use has been largely replaced by monoclonal anti-CD20 therapy.

10.2.2 Surgery and radiotherapy

The role of surgery and radiotherapy in the treatment of PTLD is limited to localized disease, especially in early type PTLD and mostly combined with RIS. Besides these treatment options can be used in case of local complications like bleeding, pain and compression. [71,99,112,113] In primary central nervous system (PCNSL) PTLD, radiotherapy and chemotherapy may both lead to a high response rate.[72,114,115] Although rituximab hardly crosses the blood-brain-barrier (BBB), case reports have shown promising results with the use of systemic rituximab in the treatment of PCNSL-PTLD, probably due to disruption of the BBB in patients presenting with central nervous system malignancies. However, the exact value of systemic or intrathecal rituximab needs to be determined taking into consideration the fact that in most cases anti-CD20 therapy was combined with other treatments.[116,117]

10.2.3 Chemotherapy

In most lymphoproliferative disorders in immunocompetent patients chemotherapy remains the cornerstone of therapy, often combined with lymphoma-specific immunotherapy. As a consequence chemotherapy (mostly CHOP or a CHOP-like regimen) has been considered for many years standard therapy in PTLD not responding to RIS. However, due to the immunocompromised state of the patient treatment related mortality, especially infectious, is substantially higher in this population, even though the use of broad spectrum antibiotics and G-CSF clearly has reduced the complication rate of chemotherapy.[118-120] Till now only one uncontrolled prospective trial has been published reporting the effectiveness of low dose chemotherapy in pediatric PTLD patients, leading to an overall response rate of 83% and a 2-year overall survival rate of 73%.[121] In adults all currently available evidence regarding the use of chemotherapy is based on retrospective data.[122] In an analysis of the Israel Penn International Transplant Tumor Registry outcome with different chemotherapy schedules were compared. Treatment with CHOP chemotherapy was associated with a 5 year overall survival of 24% with a PTLD-specific mortality of 34%, whereas single agent chemotherapy appeared to be inferior compared to combination chemotherapy.[118] One other approach may be sequential therapy using RIS, interferon-α and systemic chemotherapy, leading to lower tumor burden before start of

chemotherapy. This approach showed promising results in two prospective trials.[102,109] However, as described below, results and especially tolerance may be improved by substituting IFN-α by anti-CD20 monoclonal therapy.
Taken together we can conclude that, despite high initial response rates using chemotherapy after failing of RIS, toxicity and long term outcome remain problematic. However, in case of aggressive presentation of high grade lymphomas, including plasmablastic NHL, Burkitt and Burkitt-like NHL and T-cell NHL, and in case of Hodgkin or Hodgkin-like lymphoma, for which no immunotherapy is available, upfront chemotherapy needs to be considered.

10.2.4 Monoclonal anti-B cell therapy

During the last decade monoclonal anti-B-cell antibodies have emerged as a powerful treatment modality in most B-cell lymphoproliferative disorders, both indolent and aggressive. Consequently this new kind of immunotherapy was also investigated in the treatment of PTLD, most of which express CD20. Before the advent of rituximab combination of murine anti-CD21 and anti-CD24 monoclonal antibodies showed encouraging results in B-PTLD.[123] Most experience however has been obtained with rituximab, a chimeric murine/human anti-CD20 antibody, with numerous case reports, case series and larger retrospective analyses found in the international literature.[122] Besides five prospective trials have been published till now assessing the role of rituximab in PTLD, showing overall response rates ranging between 44% and 64%.[124-128] Most patients were treated with the standard rituximab dose of 375 mg/m²/week during 4 consecutive weeks, although Gonzalez-Barca *et al* introduced the concept of risk adapted extended treatment with rituximab in case of partial response following 4 weekly admissions. With this approach the number of complete responders was upgraded from 34% after 4 admissions to 60.5% following 8 doses.[127]
Although treatment with rituximab is associated with a high response rate in PTLD, it is important to keep in mind that it does not improve (virus-specific) cellular immunity necessitating the need for simultaneous RIS.[129] Conversely, severe B-cell depletion due to treatment with rituximab was not associated with diminished EBV-specific T-cell immunity in non-transplanted patients presenting with lymphoproliferative disorders.[130]
Although toxicity of rituximab seems to be rather low in the different retrospective and prospective trials, caution is warranted based on recently described infectious complications in non-transplant related lymphoproliferatieve disorders, including progressive multifocal leucoencephalopathy and hepatitis B reactivation.[131,132]

10.3 Anti- EBV therapy

10.3.1 Antiviral therapy

As the majority of PTLD cases are associated with EBV related lymphocyte proliferation, the use of antiviral treatment was already explored almost thirty years ago.[133] The efficacy of classical antiviral drugs in the treatment of PTLD however has been very controversial. Nucleoside analogues, including aciclovir and ganciclovir, inhibiting replication of many herpes viruses, have shown *in vitro* and *in vivo* resistance against EBV related malignancies as most of these tumors do not express viral thymidine kinase (TK). Some case reports or small series have shown limited curative potential of these antiviral agents[134], which could be explained by some degree of lytic replication in PTLD although the effect of other

simultaneous interventions might have influenced the responses. In the above mentioned study on the use of sequential RIS, interferon-α-2B and chemotherapy, all 16 patients received intravenous acyclovir during the period of RIS, without any response.[102] Of interest, prophylactic treatment with nucleoside analogues during three months following heart transplantation was associated with reduced PTLD risk in the Spanish registry.[135,136] This effect was also observed in a multicentric case-control study of kidney transplant recipients. The authors showed that antiviral prophylactic treatment was associated with a significant decrease in the risk of PTLD, especially in the first year posttransplant.[137] Experience with other antiviral agents like foscarnet and cidofovir, which act independently of the viral TK, is very limited. Oertel *et al* reported on their experience with foscarnet in three patients. All three patients achieved a complete remission, correlating with the expression of BZLF1/ZEBRA protein, which is an early antigen of lytic EBV activity.[138]

10.3.2 Intravenous immune globulins

The use of intravenous immune globulins (IVIG) might be another attractive therapy in PTLD, based on the presence of antibodies against EBV proteins. However, literature is limited to some isolated case reports in which IVIG is combined with different other therapies.[139] There is some more data available regarding IVIG prophylaxis following transplantation, though the results are very conflicting. Opelz *et al* examined the effect of anti-CMV prophylaxis on the occurrence of PTLD in a large registry study. The first year following kidney transplantation no case of PTLD was seen in patients who received anti-CMV IVIG compared to patients with antiviral agents or without prophylaxis. After the first year this difference disappeared. The authors conclude that anti-CMV IVIG might posses a broad range of anti-EBV activity.[140] On the other hand Green *et al* performed a randomized controlled trial in pediatric liver transplant patients, revealing no significant effect of the use of anti-CMV IVIG on occurrence of PTLD.[141] As a consequence it remains a matter of debate whether IVIG should be incorporated early in transplant programs.

10.3.3 Arginine butyrate

Recently very promising results have been described treating fifteen refractory EBV related malignancies –including 6 PTLDs- with arginine butyrate, resulting in pharmacological induction of viral TK. As this approach makes the tumor sensitive to treatment with nucleoside analogues, ganciclovir is added. With this combination therapy an overall response rate of 83% was observed in the PTLD subgroup with an acceptable toxicity profile.[142]

10.4 Retransplantation

In patients successfully treated for PTLD, but with loss of their graft due to reduced immunosuppression, retransplantation may be feasible. Birkeland *et al* reported on 5 kidney transplant recipients who underwent retransplantation without any sign of disease recurrence up to three years after transplantation.[143] In another small series Karras *et al* described six other cases without disease recurrence with a median posttransplant follow up of 30 months.[144] The largest published series was based on the OPTN/UNOS database, in which 69 patients with a history of PTLD underwent retransplantation. Time from PTLD to retransplantation ranged from < 1 year to 5-10 years. Immunosuppressive therapy was very similar to regimens used after first transplants. Patient and graft survival was very good, although outcome seemed to be better in abdominal organ retransplantation.[145]

11. Prognosis

In general the prognosis of PTLD is poor compared to 'similar' lymphoproliferative disorders in immune competent patients. In kidney transplant recipients 5 year overall survival following diagnosis of PTLD ranges from 40% to 60%, with the lowest survival rates in patients presenting with CNS involvement.[10,73]

Although several prognostic scores have been proposed by different authors, validation of this scores in different transplant populations have not been done or have shown conflicting results, partially due to heterogeneity in patient population and treatment.[74,128,146-149] However poor prognostic factors in immunocompetent lymphoma patients, including higher age, advanced disease, poor performance state and elevated lactate dehydrogenase, have also shown their value in outcome prediction of PTLD patients. Table 4 gives an

Score	Population	Number of patients	Treatment	Risk factors
International Prognostic Index (IPI)[146]	Immunocompetent patients with aggressive NHL	2031	Anthracyclin based combination chemotherapy	age, LDH, stage, performance state, number of extranodal sites
Leblond[147]	SOT	61	Heterogenous	Performance state, number of involved sites
Ghobrial[148]	SOT	107	Heterogenous	Performance state, monomorphic subtype, graft involvement
Choquet[128]	SOT	60	Heterogenous	Age, performance state, LDH
Hourighan[149]	Kidney	42	Heterogenous	LDH, B-symptoms
Evens[74]	SOT	80	Heterogenous	No rituximab therapy, CNS involvement, number of extranodal sites, albumin, bone marrow involvement

Table 4. Prognostic scores in PTLD

overview of the different proposed prognostic scores. Cesarman *et al* reported a poor response to RIS in patients showing bcl-6 mutations.[150] This finding, however, has not been examined in other studies.
New and especially validation of prognostic factors, both clinical/biochemical and molecular, may lead to better risk stratification in PTLD.

12. Future

Although we have learned a lot about all different aspects on PTLD during the last decades, even more questions remain. Further research and clinical studies are needed in this rapidly changing field with increasing transplant activities worldwide and the use of new and very potent immunosuppressive therapy.
Table 5 summarizes our current knowledge of PTLD and defines future opportunities which can only be possible by close cooperation between all departments involved in transplant patient care (transplantation unit, clinical hematology/oncology, pathology, radiology, nuclear medicine, immunology and virology) and between the different transplant centers.

Aspect	Knowledge	Future perspectives
Incidence	2%	Nationwide prospective and complete registry,…
Risk factors	Type of organ, EBV R-/D+, intensity immunosuppression	Measuring 'overall immune suppression', further search for specific role of immunosuppressive agents,…
Pathogenesis	80-85% EBV related	Role of other viruses, molecular pathways (gene expression profiling, single nucleotide polymorphism analysis, comparative genome hybridisation arrays,…),…
Diagnosis	Biopsy, WHO 2008	Non-invasive diagnosis? Role of PET/CT scan, role of magnetic resonance imaging,…
Staging	CT scan, bone marrow examination	Role of PET/CT scan, role of magnetic resonance imaging,…
Prevention	Serial monitoring EBV PCR?	Standardisation of EBV PCR, determination cut off value, role of HLA, cytokine gene polymorphisms,…
Therapy	Heterogenous	Prospective studies, international working group consensus,…
Prognosis	Poor	Identification of new (clinical and non-clinical) prognostic markers, prospective validation of prognostic scores,…

Table 5. Current knowledge and future perspectives in PTLD

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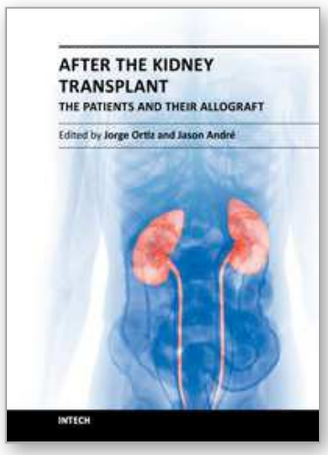

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There are many obstacles in kidney transplantation. For the transplant team, there is the balance between immunosuppression to aid in the recipientâ€™s tolerance of the allograft and the infection risk of a suppressed immune system. These potential long term complications of kidney transplantation are relatively well known, but there are many other complications that patients and families do not consider when preparing themselves for a kidney transplant. Although the benefits of attempting a kidney transplant far outweigh downfalls of the long term sequelae, kidney transplantation is by no means a benign procedure. It is the hope of these authors that the reader will leave with a sense of understanding towards the kidney recipients.

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