Classification and Treatment of Posttransplant Lymphoproliferative Disorders

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ABSTRACT: Posttransplant lymphoproliferative disorders (PTLDs) are defined by the 2008 World Health Organization classification. Monomorphic PTLD is the most frequent form; it is usually diagnosed several years after transplantation and nowadays is positive for Epstein–Barr virus in only 50% of cases. Although preventive treatments are not effective, in cases of Epstein–Barr virus reactivation, a preemptive approach can prevent the development of PTLD. The first-line curative treatment consists of reducing immunosuppression, where possible, and this alone can cure PTLD. If this fails, rituximab monotherapy is safe and induces complete remission in one-third of cases. If complete remission is not achieved, four cycles of R-CHOP [cyclophosphamide, hydroxy doxorubicin, vincristine (Oncovin®), and prednisone plus rituximab] are generally sufficient.

KEYWORDS: posttransplant lymphoproliferative disorders, Epstein–Barr virus, rituximab, R-CHOP

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Introduction

Posttransplant lymphoproliferative disorders (PTLDs) represent a group of diseases that are clearly defined by the World Health Organization (WHO) classification. The epidemiology of PTLD has evolved over the past two decades, with nowadays a generally later onset (mainly several years postgraft) and Epstein–Barr virus (EBV) being present in only 50% of cases of PTLD instead of 100% in initial reports. Despite the scarcity of the disease, a number of prospective studies have been published since 2006, and current treatments achieve survival rates similar to those of immunocompetent patients. The purpose of this review is to provide a number of practical approaches to present-day management of PTLD.

Classification and Definitions

PTLDs are defined as lymphoproliferations, which may or may not be clonal, may or may not be associated with EBV, and develop following transplantation of a solid organ or allogeneic stem cells. The WHO classification of 2008 clearly identifies PTLD, grouping them into early lesions, polymorphic PTLD, monomorphic PTLD, and classical Hodgkin lymphoma-type PTLD, as presented in Table 1.[1] EBV-encoded RNA staining is mandatory in the work-up of suspected PTLD.

Early lesions. These are mass lesions with preserved architecture of the tissue involved. Florid follicular hyperplasia is also classed in this section. Early lesions usually occur during primary EBV infection in children or EBV-seronegative adults in the tonsils or lymph nodes but rarely in extranodal localizations.

Plasmacytic hyperplasia is characterized by numerous plasma cells and small lymphocytes.

Infectious mononucleosis-like PTLD manifests paracortical expansion and numerous immunoblasts against a background of plasma cells and T lymphocytes.

The immunophenotype shows polyclonal B cells and plasma cells and T cells with no phenotypic aberrancy. EBV is present in all infectious mononucleosis-like PTLD and nearly all plasmacytic hyperplasia. Molecular genetic analysis has shown that BCL6 can be mutated whereas other oncogene mutations are absent.[2]

Polymorphic PTLD. As the name suggests, these PTLDs are morphologically polymorphic lesions, comprising the full range of B-cell maturation with immunoblasts, plasma cells, and small- and intermediate-sized lymphocytes. Polymorphic PTLDs sometimes mimic Hodgkin lymphoma, as an entity previously known as *Hodgkin-like PTLD*, with Reed–Sternberg-like cells that are $CD30^+$ but $CD20^+$ and $CD15^-$. The large majority of polymorphic PTLD are EBV positive, and this is an important feature that differentiates PTLD from graft rejection. The tumor may be polyclonal, monoclonal, or oligoclonal.

Monomorphic PTLD. This is the most frequent form of PTLD. Although proliferation is classically monotonous, pleomorphic cell morphology can be observed. Histological

Table 1. WHO classification of PTLD (2008).

TYPE OF LESION	TISSUE ARCHITECTURE	CLONAL	EBV
Early lesions			
Plasmacytic hyperplasia	Respected	No	≤100%
Infectious mononucleosis-like PTLD			100%
Polymorphic PTLD	Destroyed	No or yes	≤100%
Monomorphic PTLD			
B-cell neoplasms			50%
Diffuse large B-cell lymphoma			
Burkitt lymphoma			
Plasmacytic neoplasm			
Plasmocytoma-like lesion	Destroyed	Yes	
Other (not indolent)			
T-cell neoplasms			1/3
Peripheral T-cell lymphoma, NOS			
Hepatosplenic T-cell lymphoma			
Other			
Classical Hodgkin lymphoma-type PTLD	Destroyed		≤100%

criteria correspond to those of lymphomas developing in immunocompetent patients.

Monomorphic B-cell PTLD. Nonplasmacytic neoplasms are CD20$^+$, CD19$^+$, CD79a$^+$, and often CD30$^+$ without necessarily an anaplastic morphology. Most cases of this form of PTLD are of a nongerminal-center type,[3] particularly those which are EBV positive, whereas EBV-negative cases are more likely to have a germinal-center profile.[4] EBV is positive in 50% of cases, chiefly in early PTLD and far less frequently in late onset forms. When it is present, EBV is clonal in episomal forms.[5] Immunoglobulin (Ig) heavy-chain genes are usually mutated.[2] Using molecular genetic analysis, oncogenes and tumor suppressor mutations (such as *ras*, *Myc*, and *p53*) can be found, and BCL6 hypermutation is common,[6] the latter also being found in normal postgerminal-center B lymphocytes.

Monomorphic T/natural killer-cell PTLD. These rare entities account for 10% of all PTLD and belong mainly to the peripheral T-cell lymphoma not otherwise specified subtype.

Classical Hodgkin lymphoma-type PTLD. This form of PTLD fulfills the criteria for classical Hodgkin lymphoma found in immunocompetent patients. The main differential diagnosis is the Hodgkin-like form of polymorphic PTLD. The tumor is nearly always EBV positive.

Transition forms. It is sometimes difficult to characterize PTLD when there is both early and polymorphic or both polymorphic and monomorphic morphology in the same biopsy. These forms represent a sort of continuum between two types of PTLD.

Early and late PTLD. By convention, early PTLD (not to be confused with so-called *early lesions*) are defined by a period between the graft and the diagnosis of PTLD of less than one year. Other cases are known as *late PTLD*.

Epidemiology

Overall risk of PTLD. Lymphoma is the second most common form of cancer after skin cancer, in transplanted patients. Out of 175,732 solid organ grafts, the incidence of cancer was 1375/10^5 patients/year, this incidence represents a standardized incidence ratio (SIR) of 2.1, compared with immunocompetent patients. Lymphoma was the most frequent cancer, with an incidence of 194/10^5/year and SIR of 7.54.[7] In one retrospective study of over 164,000 transplantations, the overall risk of PTLD was seen to increase, between 1987 and 1999, the risk to develop a PTLD at five years was 4.2%, and between 2000 and 2008 it rose to 4.4% ($P = 0.006$).[8]

Risk according to graft type. The risk of PTLD varies according to the type of organ transplanted and is likely affected by the type of immunosuppressive regimen used and the amount of lymphoid tissue in the graft. Analysis of the outcomes following different transplantations shows that after 1316 kidney transplantations, the incidence of PTLD was 1.9%,[9] after 834 liver transplantations, the incidence was 2.8%,[10] after heart transplantation, the incidence was 6.5%, and after heart and lung transplantation, the incidence was 5.2%.[11] The risk associated with allogeneic stem cell transplantation (ASCT) depends on the origin of the stem cells, ranging from 1.16% in the case of matched familial donors to 2.86% in the case of mismatched familial donors and 3.97% in the case of matched nonfamilial donors to 11.24% with mismatched nonfamilial donors,[12] and 2% after cord blood transplantation.[13] A four-item score to predict PTLD development after ASCT has been proposed (Table 2) based on T-cell depletion, use of antithymocyte globulin, human leukocyte antigen (HLA) mismatch, and age.[14]

Risk according to graft survival. As long as a solid organ transplant is functional, the patient continues to require immunosuppression, and the risk of PTLD persists.[7] With long-term follow-up, the risk for a liver graft is 4.7% at 15 years[15] and the risk for a heart transplant is 15% at 13 years,[11] but only 1% at 10 years for an ASCT, thanks to the withdrawal of immunosuppression.[16]

Table 2. Predictive score for PTLD development after ASCT (according to Landgren et al[14]).

CRITERIA	RISK OF PTLD DEPENDING ON THE NUMBER OF CRITERIA
T-cell depletion Use of ATG ≥2 HLA mismatch (treated by ATG or T-cell depletion) ≥50 years old	0 = 0.2% 1 = 1.1% 2 = 3.6% 3–4 = 8.1%

Abbreviations: PTLD, post-transplant lymphoproliferative disorders; ASCT, allogeneic stem cell transplantation; ATG, antithymocyte globulin.

Risk according to age. Because of the increased incidence of EBV primary infection in adolescents and young adults, PTLDs are more frequent in children. Among 1316 kidney transplantations, the incidence of PTLD was 10.1% in children and 1.2% in adults;[9] similarly, after 834 liver transplantations, these figures were 6.7% and 1.4%, respectively.[10] In adults, there appears to be a trend toward a decreasing risk with age, as demonstrated by the outcomes of more than 164,000 transplantations: the five-year risk of PTLD was 1.74%–3.28% before the age of 34 and 0.36%–2.22% beyond the age of 50.[8]

Risk according to immunosuppression. As seen previously, T-cell depletion represents a major risk factor for PTLD following ASCT, although the risk depends on the specificity of the depletion: the more T lymphocytes are specifically destroyed, the greater the risk of PTLD is. For ASCT, selective T-cell depletion is associated with an increased relative risk (RR) of 8.4–15.8, whereas broad lymphocyte depletion (T and B cells) with alemtuzumab, an anti-CD52 monoclonal antibody, or by elutriation is associated with a RR of 3.1–3.2.[14] Similarly, in the setting of solid organ transplantation, the RR was 43.1 with a specific anti-T-lymphocyte antibody targeting CD3.[16]

It is still unclear whether different immunosuppressive drugs have different effects on the development of PTLD. However, at least one study has shown that azathioprine, a purine analog inhibiting nucleotide synthesis, is associated with a higher risk than mycophenolate mofetil, an inhibitor of the inosine monophosphate dehydrogenase that inhibits guanine synthesis.[17]

Risk according to HLA typing. Although it is tempting to search for HLA involvement in the development of PTLD, publications on the subject are contradictory. One study reported a protective effect of DR7 and A03 and an increased risk with B18 and B21 in a group of 155 solid organ transplantation (SOT) recipients who developed PTLD,[18] whereas in another study, an increased risk of EBV-positive PTLD was found with B38 and A26 but a decreased risk with A1, B8, and DR3,[19] and a third group did not find any association with HLA class I.[20]

Management

Preventive treatment. In PTLD management, the prevention refers to the treatment used before PTLD onset and EBV reactivation. It focuses essentially on anti-EBV drugs or Igs. Preventive treatment can concern all transplant patients or only those at risk. One kidney transplant study showed that for every 30 days of ganciclovir treatment, the risk of PTLD during the first year after transplantation was 38% lower, with an odds ratio of 0.62 [95% confidence interval, 0.38–1.0].[21] In a vast retrospective study on 44,828 recipients of deceased-donor kidney transplants, patients who received no viral prophylaxis were compared to patients receiving acyclovir or ganciclovir and to patients treated with anticytomegalovirus (anti-CMV) Ig (solutions enriched in anti-EBV Igs) for one year.[22] During the first year, the SIR of PTLD was similar in patients without prophylaxis and in those on antiviral drugs (respectively, 26.4 and 24.2). The 2103 patients who received anti-CMV Ig did not develop PTLD during the first year and reached the same risk level as the two other groups during the subsequent five years of follow-up. However, in a small (82 patients) but prospective study of pediatric liver transplant recipients, anti-CMV Ig provided no more protection than placebo.[23]

Preemptive treatment. Preemptive treatment concerns patients with EBV reactivation or primary EBV infection. In this setting, disease management is based on frequent (usually monthly) EBV viral load (VL) measurements. If the receiver was EBV negative at the moment of transplantation, treatment should begin as soon as EBV VL is seen to be positive. However, in the majority of cases, it is a question of a reactivation, and the primary unresolved issue is the threshold above which treatment should be initiated. As shown in Table 3, EBV VL units and thresholds vary widely in the literature. Nowadays, whole blood EBV VL is used, and despite recommendations by the WHO to express results in international units,[24] the majority of centers still use copies per milliliter. The first step in preemptive treatment is immunosuppression reduction (ISR) when possible. If this prove ineffective, rituximab, a monoclonal anti-CD20 Ig, has been shown to be highly effective, generally with one single injection. In a prospective study of 299 heart transplant patients, we used ISR when the EBV VL was over 10^5 copies/mL and added rituximab if this failed or directly in association with ISR if EBV VL was over 10^6 copies/mL (Fig. 1).[25] With this algorithm, all cases of EBV reactivation or primary infection were controlled, and no patients developed PTLD. Table 3 shows varying published preventive or curative attitudes, depending on EBV VL.[23,25–37]

Immunosuppression reduction. ISR is the widely acknowledged first-line approach, when possible. In the literature, it has been shown to lead to a complete response (CR) in up to 10% of patients in three to six weeks.[38,39] In our series of 123 cases of PTLD, five (4%) cases achieved a CR after ISR (personal data). However, there are no clear guidelines for ISR in terms of which drug can be titrated down or withdrawn. When PTLD is not life threatening, the physician should wait three to four weeks before reassessing the patient and, in the absence of a response, choosing an alternative treatment.

Table 3. Preventive and curative treatment of Epstein-Barr virus reactivation or primary infection.

REFERENCE	THRESHOLD	ORGAN	N	PI/ReA	PTLD	PREVENTIVE	CURATIVE
McDiarmid 1998[26]	≥10 copies/μg DNA	SOT (pediatric)	40	64–83%	2/40	Gan & Acy	DIS
Rooney 1998[27]	>2000 copies/ 10^6 PBMC	ASCT (pediatric)	39	–	0	Anti-EBV DLI	–
Baldanti 2000[28]	>1000 copies/ 0.5 μg DNA	ASCT	32	31.2%	0	–	DIS
Gustafsson 2000[29]	≥4 log copies/ 10^6 PBMC	ASCT	9	56%	1	–	Donor CTL
Stevens 2001[30]	>2000 copies/mL	SOT (lung)	14	–	6	–	–
Comoli 2002[31]	≥1000 copies/10^5 PBMC	SOT	7	–	–	–	Autolo-gous CTL
van Esser 2002[32]	>1000 copies/mL	ASCT	49	31%	–	Rituximab	–
Lee 2005[33]	≥4000 copies/μg DNA	SOT (liver—pediatric)	73	26%	2%	–	DIS
Humar 2006[34]	≥1000 copies/10^6 PBMC	SOT	16 14	56.3% 33.3%	8.8%	Gan Gan + Ig	–
Green 2006[23]	≥2000 copies/10^6 PBMC	SOT (liver—pediatric)	43 39	29% 21%	16% 9%	Placebo IgA CMV	–
Savoldo 2006[35]	≥1000 copies/μg DNA	SOT	12	15.5%	0	Autologous CTL	–
Bakker 2007[36]	>10000 copies/mL	SOT (lung)	75	25%	1.5%	–	DIS + Val
Worth 2011[37]	>40000 copies/mL	ASCT	70	28.6%	1.4%	–	Rituximab
Choquet 2014[25]	>10^5 copies/mL	SOT	299	12%	0.3%* 0%†	–	DIS ± rituximab

Notes: *Intent to treat, †per protocol.
Abbreviations: Acy, aciclovir; CTL, cytotoxic T lymphocytes; DIS, decrease of the immunosuppression; DLI, donor leukocyte infusion; EBV, Epstein-Barr virus; Gan, ganciclovir; ASCT, allogeneic stem cell transplant; Ig, immunoglobulin; PBMC, peripheral blood mononuclear cell; PI, primary infection; PTLD, post-transplant lymphoproliferative disorder; ReA, reactivation; SOT, solid organ transplantation; Val, valganciclovir.

Antiviral drugs. The use of antiviral agents as a treatment for PTLD remains controversial. Latently infected cells, found in the vast majority of PTLD, are not impacted by antiviral agents, such as valacyclovir, acyclovir, ganciclovir, and valganciclovir, which need EBV protein kinase to inhibit lytic viral production.[40] However, foscarnet, an inhibitor of viral-DNA polymerase, has been described in one case report as potentially effective.[41]

Chemotherapy and rituximab. Although the response rate with chemotherapy is good, treatment-related mortality (TRM) remains high. In a homogeneous retrospective series of 25 patients treated by CHOP [cyclophosphamide, hydroxy doxorubicine, vincristine (Oncovin), and prednisone], the CR and overall survival (OS) rates were 48% and 67%, respectively, but one-third of the patients died of toxicity.[42] In this context, the first prospective study of PTLD assessed patient response to four weekly injections of rituximab. Eighty days after the end of treatment (43 patients), the response rate was 44%, and the CR rate was 28%; there was no TRM.[43] In an attempt to improve on these results, a Spanish team added four further weekly doses of rituximab in the event of a partial response. They observed a CR in 10 out of 12 patients, leading to an OS rate of 47% at 27 months for the entire population treated.[44]

Sequential treatment. In a prospective study, the European PTLD network proposed adjuvant therapy with CHOP every 21 days (CHOP-21) four times after the four rituximab injections. The overall response rate was 60% after rituximab (CR rate, 20%) and 90% after R-CHOP-21 (rituximab + CHOP-21); median progression-free survival was four years, and median OS was 6.6 years, which is the longest ever published. TRM was 10.6%, ie, similar to previous studies.[45] Because patients showing a CR after rituximab had better outcomes in this study and generally remained in CR with rituximab monotherapy, the latest European prospective protocol has proposed a treatment regimen according to the response to rituximab: in cases of CR, patients receive four further rituximab injections every 21 days; all other patients receive four courses of R-CHOP-21. The results of this protocol have not yet been published but were presented as an oral presentation; they clearly demonstrate similar CR rates but with lower toxicity.[46]

Pediatric PTLD. In pediatric populations, low-dose chemotherapy appears effective with limited toxicity. Very good results have been reported with a protocol based on cyclophosphamide, prednisone, and rituximab;[47] after two years, event-free survival was 71%, OS rate was 83%, and TRM was 5%.

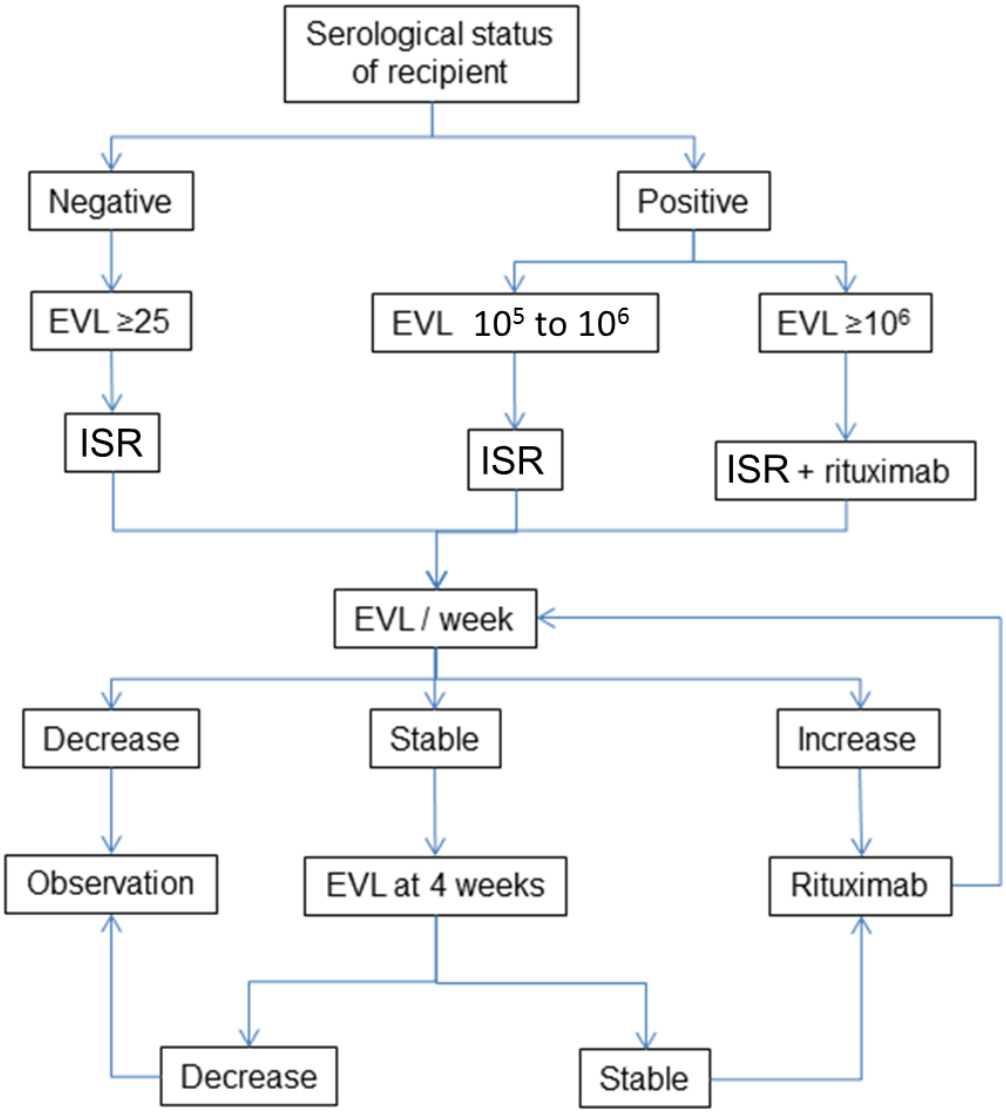

Figure 1. Epstein-Barr virus reactivation or primary infection preemptive treatment algorithm.
Note: Rituximab administered in one infusion of 375 mg/m².
Abbreviations: EVL, Epstein-Barr virus viral load (copies/mL), technique is described in;[25] ISR, immunosuppression reduction.

PTLD of the central nervous system. Although approximately 10% of PTLD are localized in the central nervous system (CNS), no prospective studies have been published in this field. The most recent study conducted a retrospective analysis of 84 cases of CNS PTLD.[48] Although treatment was not identical in all patients, most underwent ISR, and half received high-dose methotrexate. In univariate analysis, there was a trend toward a greater benefit from treatment with rituximab ($P = 0.09$) and high-dose cytarabine ($P = 0.08$). The response rate was 60%, with TRM at 13%; three-year progression-free survival and three-year OS rates were 32% and 43%, respectively. Whole-brain irradiation is an effective option, though late CNS complications are frequent and age dependent.

Post-ASCT PTLD. As the onset of PTLD after allogeneic hematopoietic stem cell transplantation AHSCT nearly always occurs soon after transplantation, ISR is difficult or impossible to achieve, and chemotherapy is particularly toxic for the new marrow. Rituximab monotherapy has been shown to be the most effective first-line therapy;[49–51] the number of injections required has not been clearly defined, but four weekly courses are usually sufficient.

CD20-negative PTLD. PTLD of Hodgkin- or multiple myeloma-type should be treated in the same way as the respective diseases in immunocompetent patients, following ISR. Plasmacytic PTLD can benefit from conventional radiotherapy or chemotherapy that is effective in lymphoma.[52] In a pediatric population, an early-onset, EBV-negative form of plasmacytic PTLD was shown to respond well to dexamethasone or thalidomide.[53]

Relapsed/refractory PTLD after solid organ transplantation. There are no treatment guidelines in this field.

Classic second-line chemotherapy and even autologous stem cell transplantation can be used. One direction for future research could be anti-EBV cytotoxic T lymphocytes (aEBV CTL). Although this approach is not yet available outside study settings, a number of encouraging results have already been published. Donors are generally not available, but allogeneic aEBV CTL from healthy donor banks are a potentially promising option. In one series of 33 patients, the authors reported 12 CR and 9 partial responses.[54]

Relapsed/refractory PTLD after ASCT. Donor lymphocytes should be used if the donor is EBV positive but unmodified donor CTL injections are to be avoided. Donor lymphocyte injections have been seen to be toxic, inducing severe graft-versus-host disease.[55,56] Stimulation and amplification of donor-derived anti-EBV CTL is an effective and relatively safe alternative treatment. Basic protocols require three to four weeks amplification on EBV-positive lymphoblastic cell lines, and injection induces durable responses and prolonged in vivo amplification.[27,57] Faster protocols have recently been proposed with overnight stimulation of donor mononucleated cells by EBV-specific peptides followed by aEBV CTL selection. A positive response to treatment was observed in three out of six PTLD patients,[58] and in one case after haploidentical ASCT.[59] In the particular case of cord-blood ASCT, donor cells are not available, so allogeneic aEBV CTL from a healthy-donor bank is the treatment of choice where possible. When aEBV CTL are not available, chemotherapy is the last resort.

Conclusion

The specific pathophysiology of EBV-positive PTLD means that they can be avoided with preemptive treatment. However, EBV-negative cases do not benefit from this approach. Even if the histology of overt PTLD is similar to that of classic non-Hodgkin lymphoma, it requires specific management. The key features for optimal outcomes are ISR, rituximab, and a limited number of courses of chemotherapy. Progress has yet to be made with regard to the treatment of CNS PTLD, such as the publication of expert consensus treatment guidelines. The near future is likely to see the development of cellular therapy, particularly targeting EBV-positive PTLD.

Author Contributions

Conceived the concepts: SC. Wrote the first draft of the manuscript: SC. Developed the structure and arguments for the paper: SC. Made critical revisions: SC. The author reviewed and approved of the final manuscript.

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