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EBV post-transplant lymphoproliferative disorder – update on management and outcomes

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Abstract

Purpose of Review—Management of Epstein-Barr virus post-transplant lymphoproliferative disorder (EBV PTLD) is complex, involving risk stratification, prevention and/or pre-emptive measures involving monitoring EBV DNAemia and balancing treatment options, using a combination of reduction of immune suppression, anti-B cell therapy, and cytotoxic T lymphocytes (CTLs).

Recent Findings—The highest risk factor for the development of EBV PTLD in hematopoietic cell transplant (HCT) remains T cell depletion, with increasing use of anti-thymocyte globulin (ATG) or alemtuzumab in conditioning. In solid organ transplantation (SOT), the incidence of PTLD is highest among EBV seronegative recipients who are at risk for primary EBV infection following transplant in the first 12 months. Prevention is a critical component of the management of EBV PTLD. Although pre-emptive therapy remains standard of care, there continues to be heterogenicity and debate over the optimal choice of EBV DNA quantification and the threshold to use. Novel therapies such as donor-derived multi-pathogen and EBV specific CTLs for the prevention and third party CTLs for the treatment of EBV-PTLD are promising, with rapidly expanding evidence, including large scale Phase III trials currently underway.

Summary—With an increasing number of risk groups for developing EBV PTLD in HCT and SOT, management strategies using prophylaxis or pre-emptive therapy remain standard of care, however the use of prophylactic or pre-emptive EBV specific or multi-pathogen CTLs show promising results and safety profiles.

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DECLARATION OF INTEREST

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Keywords

Epstein-Barr virus (EBV); Epstein-Barr virus post-transplant lymphoproliferative disorder (EBV-PTLD)

INTRODUCTION

Epstein-Barr virus (EBV) is a γ-herpes virus which largely causes an asymptomatic primary infection in immunocompetent hosts, establishing a life-long latent infection in B cells which is controlled by T lymphocytes and NK cells [1, 2]. Over 90% of adults and 50% of children globally are infected with EBV [2]. However, in patients undergoing allogeneic hematopoietic cell transplantation (HCT) and solid organ transplantation (SOT), EBV infects naïve B cells to transform into proliferating blasts, potentially resulting in post-transplant lymphoproliferative disorder (EBV PTLD) [3]. EBV infected B cells in SOT recipients are usually of recipient origin, while in HCT, typically of donor origin [4]. Unlike HCT, only approximately half of PTLD in SOT is EBV positive, and the majority of late presenting PTLD is EBV negative [5]. EBV PLTD is recognized as a significant cause of morbidity and mortality in this population with an associated mortality of over 50% [6, 7].

Management of EBV PTLD is complex, involving risk stratification, prevention and/or pre-emptive measures involving monitoring EBV DNAemia and balancing treatment options, using a combination of reduction of immune suppression, if possible, anti-B cell therapy, and more recently, cytotoxic T lymphocytes (CTLs). While guidelines have been updated for the SOT population in 2019 [5], the most recent management guidelines in HCT remain the 2016 European Conference on Infections in Leukemia (ECIL-6) guidelines [3]. This review aims to summarize the most recent developments on the new risk groups for developing EBV PTLD, monitoring and diagnostic approaches, prevention strategies and treatment options.

NEW RISK GROUPS AND RATE OF EBV VIREMIA AND PTLD IN SPECIFIED POPULATIONS

HCT risk groups

The most significant risk factor for the development of EBV PTLD in HCT is *in vivo* T cell depletion, most commonly using anti-thymocyte globulin (ATG) or alemtuzumab in conditioning [8-12] (See Table 1). In a recent Center for International Blood and Marrow Transplant Research (CIBMTR) report of identified PTLD cases post-HCT, 78% were conditioned with ATG or alemtuzumab. The study demonstrated an overall survival one year post diagnosis of PTLD of 53%. Although this risk factor is not a recent development, the use of ATG in HCT practice is changing, with its use becoming more widespread, including in mismatched and matched unrelated donor (MMRD and MURD) recipients as well as increasingly in matched related donor (MRD) recipients with high GVHD risk [13-15]. One recent report of using ATG for all MMRD and MURD recipients by Ali *et al.* demonstrated a 71% reactivation of EBV (≥1000 IU/mL), however a relatively low rate of PTLD (2.4%) using a pre-emptive management approach [15].

The incidence of PTLD is low when using post-transplant cyclophosphamide (PTCy) in the setting of haploidentical donor recipients [16], with a large retrospective analysis of adult alloHSCT recipients demonstrating no PTLD at 1 year post HSCT [17]. However, a recent report of ATG in combination with PTCy for GVHD prophylaxis demonstrated a 63.7% EBV reactivation and 12% incidence of PTLD [18]. In addition, a recent large single center retrospective analysis of consecutive HCT patients by Ru *et al.* demonstrated that the two independent risk factors for EBV reactivation were haploidentical donor (HR 1.8, p= 0.001) and ATG use (HR 4.4, p<0.001), with the caveat that ATG was administered to all haploidentical donor HCTs [12].

SOT risk groups

In SOT recipients, the incidence of PTLD varies depending on donor/recipient EBV serostatus, organ(s) transplant, and immunosuppressive regimen [5]. Donor and recipient EBV serology is measured prior to solid organ transplantation as markers of latent EBV infection within the donor and pre-existing EBV-specific immunity in the recipient. When primary EBV infection occurs after solid organ transplantation, EBV-directed CD8+ T-cell responses are diminished, and latent EBV infection is established in a larger B-cell reservoir than when primary EBV infection occurs in immunocompetent hosts [19]. Thus, the incidence of PTLD is highest among EBV seronegative recipients who are at risk for primary EBV infection following transplant. The relative risk of PTLD in EBV seronegative recipients (R−) versus EBV seropositive recipients (R+) ranges from 2.6-9.9 [20, 21]. Recipient EBV seronegativity is more common in pediatric (~55%) compared to adult (~10%) SOT recipients and children therefore have a higher incidence of PTLD [20, 22]. Latently infected donor B-cells often travel with solid organ allografts from EBV seropositive donors (D+) and serve as an important source of primary EBV infection in seronegative recipients. In adults, PTLD incidence among EBV donor positive, recipient negative (D+/R−) transplants is 2-3 times higher than the incidence among EBV D−/R− transplants [23].

The incidence of PTLD varies by organ transplanted and is highest among recipients of intestine (up to 20%) allografts, followed by lung (3-10%), heart (2-8%), liver (1-5%) and kidney (0.8-2.5%) [24]. The relatively high risk of PTLD in intestinal and lung recipients may be due to the abundance of lymphatic tissue within these organs (and thus a large reservoir of B-cells), coupled with the high intensity of maintenance immunosuppression required to prevent allograft rejection [19]. Induction with potent T-cell depletion using muromonab-CD3 (OKT3) or alemtuzumab is associated with a higher risk of PTLD compared to induction with ATG or anti-IL-2 receptor antibodies such as basiliximab [25]. In a Phase III randomized trial of maintenance cyclosporine versus belatacept, the T-cell co-stimulation blocking agent in kidney transplant recipients, belatacept was associated with a higher incidence of PTLD than cyclosporine in EBV seronegative patients [26]. Over half of PTLDs in patients receiving belatacept involved the central nervous system and the majority were fatal.

Of note, EBV RNA (EBER) expression does not occur in all PTLDs following SOT, and the proportion of PTLDs that are EBV-negative in SOT recipients has increased over the

past 30 years from 10% between 1990-1995 to 48% between 2008-2013 [27]. Whether EBV has a role in the pathogenesis of EBV-negative PTLD is not clear. An EBV “hit and run” hypothesis, whereby EBV infects B-cells, induces chromosomal aberrations, then exists the cell, has been proposed but has not undergone rigorous evaluation [28]. In a single center investigation of 4171 SOT recipients, the cumulative incidence of EBV-negative PTLD was higher in EBV R− compared to EBV R+ (HR 3.56, P=0.008), but the hazard ratio for development of EBV-positive PTLD was roughly 4-fold higher (HR 14.2, P<0.009) [20].

NEW MONITORING/DIAGNOSTICS

Pre-emptive approaches, standardization and kinetics of EBV DNA assay and samples

Surveillance of EBV DNAemia using nucleic acid testing remains the current standard management approach in preventing PTLD in high-risk populations. Following the detection of EBV DNAemia to a specific threshold, interventions with either pre-emptive therapy and/or a reduction of immunosuppression, if possible, are implemented [3, 5, 29] (See Table 2). However, there remains variability in the sample used to measure EBV DNAemia, including plasma, whole blood or peripheral blood mononuclear cells (PBMCs). Whilst the optimal sample is currently debated, plasma seems the most reliable marker for EBV PTLD [30]. There is also a large variation in practice for when to intervene; due to this historic heterogeneity, the ECIL guidelines for HCT have not recommended a specific threshold of when to intervene, with EBV DNAemia ranging from 1000 copies/mL to 40,000 copies/mL recommended. However, with the implementation of WHO international standardization (IS) of EBV measurement to international units/mL (IU/mL) in 2011, there has been a growing body of evidence for the standardization of EBV DNAemia monitoring for pre-emptive therapy [31]. Solano *et al.* demonstrated in a small cohort of T cell replete HCT recipients (ATG in 17% of patients) that plasma EBV DNA-load kinetics analyses were unlikely to be useful in predicting the occurrence of high-level EBV DNAemia, PTLD, or recurrent EBV DNAemia [32]. However, studies focusing on the viral kinetics of EBV DNAemia in T-cell deplete populations such as ATG conditioned recipients, indicated that there is a clear need to instigate pre-emptive therapy, although the ideal EBV DNAemia level to intervene remains unclear [3, 33-36], (See Table 3). Recent large single center analyses have suggested that an EBV DNA level of 1000IU/mL to 10,000IU/mL on plasma or whole blood may be an optimal pre-emptive threshold [37-39].

SOT recipients who are EBV-seronegative prior to transplant are frequently monitored for EBV DNAemia at regular intervals following transplant. Reduction of immunosuppression (RIS) in response to EBV DNAemia has been shown to reduce the incidence of early PTLD in studies of pediatric SOT recipients that use historical control groups [40, 41]. While pre-emptive RIS in response to EBV DNAemia has not been evaluated using randomized, contemporaneous cohorts, RIS during primary EBV infection theoretically promotes the development of EBV-specific T-cell responses and is frequently used as a pre-emptive strategy in both adult and pediatric EBV-seronegative SOT recipients [5].

Antiviral prophylaxis or pre-emptive therapy with acyclovir and ganciclovir, which are commonly used to prevent non-EBV herpesvirus infections post-transplant, have not been effective in preventing PTLD in SOT or HCT recipients [3, 5]. While retrospective

observational studies examining the association between antivirals and PTLD in SOT have shown mixed results, neither prophylactic nor pre-emptive antivirals were associated with a decreased incidence of PTLD in a large meta-analysis [42]. In a prospective study of pediatric liver transplant recipients in which SOT recipients received ganciclovir for 2 weeks immediately followed by 50 weeks of either oral acyclovir or placebo, there was no difference in the incidence of PTLD between groups [43]. Likewise, antivirals have not been effective in the treatment of PTLD in SOT recipients, perhaps because antivirals are most effective at targeting lytic EBV infection rather than the latently infected state characteristic of PTLD. Pharmacologic agents that induce transformation of EBV from the latent to the lytic phase, such as the histone deacetylase inhibitor arginine butyrate and the proteasome inhibitor bortezomib, sensitize latently infected B-cells to the effects of antivirals; these agents have been used in small observational trials [5].

Diagnostic strategies

The diagnostic strategy for suspected EBV PTLD includes routine blood tests, review of recent EBV DNA results, imaging and ideally a tissue biopsy [3, 5]. Imaging has traditionally been with CT scan, however PET-CT is increasingly used due to improved sensitivity and specificity, allowing for accurate staging and identification of sites for biopsy [5]. A recent analysis of the diagnostic performance of PET-CT demonstrated a sensitivity of 85%, specificity of 90% and good inter-observer reliability [44]. Biopsy of an involved site is the gold standard diagnostic test and should be performed wherever possible. Occasionally this is not feasible due to anatomical or clinical limitations, in which case treatment may be initiated for probable disease, on the basis of EBV DNA and PET-CT results [3, 5].

NEW PREVENTION STRATEGIES

Prophylaxis with Rituximab

Previous studies have demonstrated that pre-transplant rituximab safely and effectively lowers the incidence of EBV reactivation following allogeneic HCT for B-cell malignancies [45]. Thus, the role of rituximab prophylaxis for high risk HCT patients is becoming more established, as evidenced by its recommendation by a recent proposed approach by Hamed *et al.* [46-50]. For example, Van Besien *et al.* administered a single dose of rituximab 375mg/m^2 two weeks prior to haplo-cord alloHSCT unless the patient had a recent prior exposure to rituximab due to treatment for a primary B-cell malignancy. Compared to a control group, EBV reactivation occurred in 1/51 (2%) with rituximab exposure vs 27/146 (18%) without (P=0.004). PTLD developed in 16/146 (12%) without prior rituximab exposure vs none with rituximab exposure. In SOT recipients, the role of peri-transplant rituximab in preventing PTLD is less clear. The Swiss Transplant Cohort Study found no significant difference in the incidence of PTLD between SOT recipients receiving induction regimens with or without rituximab, although no patients who received rituximab developed PTLD [51].

Prevention strategies using CTLs

The most recent emerging strategy for the prevention and treatment of EBV PTLD is the use of donor derived or third party EBV-specific CTLs. The utility of CTLs has been

demonstrated for over a decade, with historical studies demonstrating approximately 95% successful elimination of EBV viremia, and 65%-88% success for the treatment of PTLD, even after the failure of rituximab-based therapy [7, 52-55]. However, access and HLA compatibility has posed a challenge for the wide applicability of their use [3]. Evidence for CTLs as a prevention strategy in SOT recipients is limited. In an observational study of 21 SOT recipients at high risk for PTLD who received autologous EBV-specific CTLs, only one patient developed PTLD [5]. Recently, multi-pathogen specific donor-derived CTLs have been described as a broad infection prevention strategy for high risk HCT recipients [56-59].

mTOR inhibitors

The use of mammalian target of rapamycin inhibitors (mTORi), particularly sirolimus, has also recently been described as a potentially beneficial agent against EBV viremia and PTLD [48]. A recent study by Hellewell *et al.* demonstrated GVHD prophylaxis with an mTORi was significantly less likely to develop an EBV DNAemia post HCT [60]. The mechanism of action for this effect is likely to be due to inhibition of the proliferation of transformed cell lines [61]. Further investigation into this effect in clinical practice is required. This effect in SOT however remains unproven despite the wide application of changing therapy to an mTORi for PTLD prevention [62].

Vaccines

A vaccine that induces adaptive EBV immunity and prevents uncontrolled primary EBV infection could offer protection against PTLD among EBV seronegative recipients. However, no such vaccine has been developed to date. A phase II trial in healthy EBV seronegative young adult SOT recipients, comparing placebo to a vaccine containing recombinant EBV subunit glycoprotein 350 (gp350) showed that the subunit vaccine induced anti-gp350 antibodies in 99% of participants and had 78% efficacy in reducing symptomatic infectious mononucleosis, but did not prevent EBV infection as assessed by anti-VCA (anti-viral capsid antigen) seroconversion [63]. EBV vaccines that induces T-cell responses may have greater efficacy in reducing primary EBV infection and are currently in development [64].

NEW TREATMENT OPTIONS

Although a reduction in immune suppression has historically been the backbone of PTLD treatment, the response rate from this strategy alone is low, and timely addition of rituximab and/or CTLs is recommended [3, 5, 65]. In SOT recipients, 44-79% of patients with CD20 positive PTLD respond to RIS and rituximab alone, and 25% will experience complete remission without any additional chemotherapy [24]. Cytotoxic chemotherapy is used for CD20 negative PTLDs or when rituximab monotherapy is unsuccessful [5]. Conversely in HCT, RIS is rarely successful as a sole intervention for the treatment of proven or probable PTLD [3], and should be combined with rituximab therapy, with response rates of 84% in patients who received both rituximab and RI, compared to 61% in rituximab alone [65].

CTLs in HCT

T cell therapies have demonstrated efficacy in the treatment of PTLD, including after rituximab failure [7, 52-55]. Unselected donor lymphocyte infusions (DLI) are a potential option, with responses in up to 70% of patients [52]. However, DLI carries a significant risk of inducing GVHD so is not commonly used in this setting. EBV specific CTLs produce at least equivalent response rates [7, 52-55], but have not been associated with GVHD, even when not HLA-matched [52, 66]. Access to these products has historically been an issue due to the timing of producing donor-derived CTLs, particularly as PTLD can be a rapidly progressive disease. A recently reported Phase II trial was able to overcome this barrier by establishing a cryopreserved bank of “third party” or “off-the-shelf” EBV-CTLs, allowing patients to be treated within 1-2 days of referral [66]. From a bank of 330 EBV-CTLs, 46 patients were treated with a response rate in HCT patients of 68% and one-year survival in responding patients of 88.9%. The promise and flexibility of CTL therapy was further demonstrated by a recent case report of a patient who successfully received five T cell infusions from three separate donors for three viral infections, including EBV-PTLD [67]. EBV CTL use is rapidly expanding with a number clinical trials emerging in recent years, including a large phase III study evaluating the use of commercially available EBV CTL in HCT and SOT (MATCH, NCT03392142 and ALLELE, NCT03394365) with promising preliminary abstracts published [68, 69], as well as a number of phase I studies in progress [52, 70].

CTLs in SOT

Data regarding EBV-specific CTLs for EBV-positive PTLD in SOT recipients is limited. Most PTLDs in SOT are recipient in origin, and HLA mismatch between donor-derived cells lines and the recipient tumor limits the efficacy of donor-derived CTLs [71]. Furthermore, lymphocytes from deceased SOT donors may not be readily available. Third-party EBV-specific CTLs with best available HLA match circumvents the issues of donor lymphocyte accessibility and donor/recipient HLA mismatch, and has been used successfully for treatment of PTLD in SOT recipients. In 33 patients receiving third-party EBV-specific CTLs for refractory EBV-positive PTLD (31 SOT, 2 HCT), 52% achieved partial or complete response at 6 months, and closer HLA matching was associated with better responses [55]. In a cohort of 10 pediatric SOT recipients with EBV-positive PTLD receiving EBV-specific CTLs, 8 (80%) achieved remission [72].

New Chemotherapy/BITE/CAR-T therapy

CD-19-directed chimeric antigen receptor-T-(CAR-T) cell immunotherapy is an effective treatment for relapsed or refractory diffuse large B-cell lymphoma (DLBCL) [73, 74]. DLBCL accounts for 90% of monomorphic PTLDs in SOT recipients and may be either EBV-positive or EBV-negative [24]. Data for efficacy of CD-19-directed CAR-T therapies for PTLD in SOT recipients is limited. In a case series of three SOT recipients who received CD-19-directed CAR-T for DLBCL due to EBV-negative PTLD, all three patients developed significant immune effector cell associated neurotoxicity (ICANS), did not achieve clinical response, and died within four months after CAR-T infusion [75]. Programmed cell death protein 1 (PD-1) and programmed cell death ligand-1 (PD-L1) are frequently expressed

in PTLD tumor cells in both SOT and HCT recipients, suggesting a future role for the treatment of PTLD, but also carries a risk of inducing graft versus host disease or solid organ allograft rejection [76]. Other potential agents in which individual case reports have described varying responses include daratumumab in rituximab-resistant, CD38 expressing EBV− PTLD following HCT [77]; zanibrutinib for CNS PTLD following HCT [78], and ibrutinib (together with CTLs) following SOT [79]. Bortezomib has also been reported in combination with rituximab [50], as well as brentuximab in CD30 expressing PTLD [80].

OUTCOMES

Despite recent advances in the prevention and treatment of EBV-PTLD, the outcomes remain poor. In a recent HCT international registry study, of 432 cases of PTLD identified, the 1-year overall survival was 53%, however only 38% of these deaths were directly attributed to PTLD [81]. In a Spanish multicenter study, 102 PTLD were identified among 12,641 HCT, leading to an estimated frequency of 0.8%. Survival was similar to the CIBMTR study, with a 2-year overall survival of 33% and the PTLD-related mortality 45% [82].

The outcomes of PTLD following SOT appear marginally better, with a report of 80 PTLD cases demonstrating a 3-year overall survival of 62%. Interestingly, patients who received rituximab-based therapy as part of initial treatment had 3-year overall survival of 73% compared with 33% without rituximab [83]. A similar report of 176 adult SOT recipients demonstrated a 2-year survival of 60% and 5-year survival of 47-49% [27].

CONCLUSION

With outcomes remaining poor after diagnosis, prevention is a critical component of the management of EBV PTLD, particularly in high-risk populations such as T-cell depleted HCT recipients and D+/R− SOT recipients. The most commonly used management strategy remains the utilization of pre-emptive therapy, however there continues to be heterogenicity and debate over the optimal choice of EBV DNA quantification and the threshold of how and when to intervene. In particular, the risk-benefit balance of over-treating with rituximab versus delaying pre-emptive treatment too long and missing the development of PTLD, which can be rapid, particularly in a T cell depleted HCT recipient. Future management strategies with prophylactic or pre-emptive EBV specific or multi-pathogen CTLs have shown promising results and safety profiles, which may be the pre-emptive treatment of choice over rituximab following the publication of current phase III trials.

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KEY POINTS:

- Prevention is a critical component of the management of EBV PTLD, particularly in high-risk populations such as T-cell depleted HCT and EBV D+/R− SOT.
- Although pre-emptive management remains standard of care, there continues to be debate and variability of practice in the optimal choice of EBV DNA quantification and the threshold to use.
- Future management strategies with prophylactic or pre-emptive EBV specific or multi-pathogen CTLs show promising efficacy and safety profiles

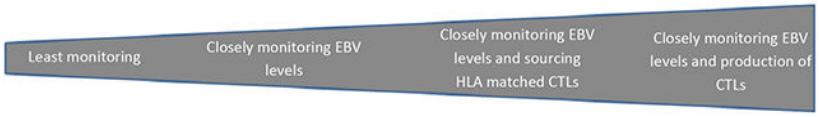
Table 1.

Risk factors for EBV PTLD in HCT and SOT

Factors which INCREASE the risk of developing EBV PTLD	
HCT [3, 10-12, 84-87]	**SOT**
Anti-thymocyte Globulin (ATG) or alemtuzumab	<12 months after transplant
In vivo T-cell Depletion	Intestine > lung > heart > liver > pancreas > kidney
EBV serology donor/recipient mismatch (recipient-negative/donor-positive)	Donor EBV+/ Recipient EBV−
Cord blood transplantation	Children
Reduced intensity conditioning	Belatacept immunosuppression
HLA mismatch	
Splenectomy	
Second HSCT	
Severe acute or chronic GvHD requiring intensive immunosuppressive therapy	
Infusion of mesenchymal stromal cells	
Factors which REDUCE the risk of developing EBV PTLD	
HCT	**SOT**
Rituximab exposure within 6 months pre-HSCT	>12 months after transplant
Post-transplant cyclophosphamide (without ATG)	Kidney > pancreas > liver > heart > lung > intestine
Sirolimus use for GVHD Prophylaxis	Recipient EBV+
CD4+ T-lymphocyte count >50 at day +30	Adults

Table 2.

Characteristics of the available strategies to manage PTLD in high-risk HCT and SOT patients

	Prophylaxis with rituximab	Pre-emptive/treatment strategy with rituximab	Pre-emptive/treatment with third party CTLs	Prophylaxis with donor-derived CTLs
General principle	Circulating anti-CD20 prevents B-cell proliferation and EBV reactivation	Anti-CD20 prevents/treats B-cell/EBV proliferation when EBV DNAemia is rising	Third party EBV specific CTLs treat EBV proliferation when EBV DNAemia is rising	Donor-derived EBV specific CTLs prevent EBV proliferation
Typical application	Administration of rituximab (200mg-375mg/m2) immediately prior to cell infusion/organ donation	Following regular (usually weekly) monitoring of EBV DNAemia, pre-emptively treating with 375mg/m2 weekly at a specific threshold to prevent the incidence of PTLD or treat early PTLD	Following regular (usually weekly) monitoring of EBV DNAemia, pre-emptively treating with HLA matched third party EBV specific CTLs at a specific threshold to prevent the incidence of PTLD or treat early PTLD	Administration of donor-derived EBV specific CTLs following cell infusion/ organ donation
Safety concerns	Minimal: Increased infection risk from B-cell depletion	Minimal: Increased infection risk from B-cell depletion	Potential concerns with GVHD/organ rejection, however this has not been proven	Potential concerns with GVHD/organ rejection, however this has not been proven
Use of rituximab				
Overall estimated cost of therapy				
Logistical challenges for application				
Level of Evidence in HCT	+	+++	+	+
Level of Evidence in SOT	+	+	+	+
Considerations		Currently no consensus for EBV assay/sample used and EBV DNAemia threshold to use for pre-emptive treatment	Large phase III and expanded access trials in commercial product (Tabelecleucel) pending, not currently FDA approved HLA matching is not always possible	Facilities to produce donor-derived EBV CTLs are uncommon The cost and turnaround time to produce donor-derived CTLs is prohibitive

*All strategies can be used in conjunction with reduction of immunosuppression following EBV DNAemia monitoring

Table 3.

Summary of recent reported EBV preventative strategies using rituximab in HCT

Study	Patients and HCT Protocol	Monitoring	Sample	Pre-emptive EBV threshold	Treatment details	EBV reactivation and PTLD rates
Jain *et al.* 2019 [37, 38]	N = 488 myeloablative and non-myeloablative HCT GVHD Px included a selection of TAC, MMF, MTX ATG 2.5-7.5mg/kg in 306/488 patients	Weekly until day 100, or beyond this if GVHD, immunosuppressants or previous EBV PTLD. Repeat testing every 3-5 days after reactivation	Whole blood	>2,000copies/mL and continues to rise on a weekly basis; OR 2,000-5,000copies/mL and considered high risk of EBV reactivation; OR >5,000copies/mL	Pre-emptive rituximab 375mg/m^2 weekly	14% (67/488) EBV reactivations as per criteria 1.4% (7/488) EBV PTLD
Van Besien *et al.* 2019 [49]	N = 198 haplo-cord donors, supplemented by CD34 selected third-party cells to accelerate recovery most commonly FluMel+/−TBI GVHD Px included TAC, MMF, ATG 4.5-6mg/kg, rituximab 375mg/m^2, 2 weeks prior to HSCT (n=38), prior treatment with rituximab (n=13), no rituximab (n=147)	Twice weekly during hospitalization, then weekly for the first 100 days, then second weekly until day180 or as clinically indicated	Not reported	Not reported, PTLD reported based on “rapid increasing EBV levels”, positive PET scan and biopsy proven PTLD	Prophylactic rituximab 375mg/m^2 was administered 2 weeks prior to HSCT (n=38) unless prior treatment with rituximab was given for primary B-cell malignancy (n=13).	Prior rituximab: 2% (1/51) EBV viremia (>200 copies/mL). No EBV PTLD No prior rituximab: 18% (27/146) EBV viremia. 12% (16/146) EBV PTLD
Ru *et al.* 2020 [12]	N = 890 Bu/Cy, TBI/Cy, Flu/Bu/Cy or Flu/Bu/Ara-C GVHD Px included CSP, MTX; MMF and ATG for URD and Haplo (27.9%)	Weekly until day +90, then fortnightly until day +180	Whole blood	10^5 Copies/mL or 10^4 Copies/mL for 2 weeks	Initially reduction in immunosuppression and treatment with ganciclovir/foscarnet, then pre-emptive treatment with rituximab (no dose given)	19.6% (175/890) EBV reactivation. 0.7% (7/890) EBV PTLD Incidence of ATG patients not reported separately. The cumulative incidence of EBV reactivation was 2.9%, 11.7%, 27.3%, and 41.9% for patients with 0, 1, 2, and 3 risk factors including ATG, haplo, and GVHD
Marzolini *et al.* 2021 [36]	N = 515 Cy/TBI or Flu/Cy/TBI GVHD Px included Alemtuzumab 20-100mg	Weekly up to day 100	Plasma	Only treated if clinical signs of “EBV disease”	Immunosuppression reduced and rituximab 375mg/m^2 was administered weekly for 4 weeks	35% (192/515) EBV reactivation. 3.9% (20/515) EBV disease, 19 PTLD, 1 EBV encephalitis.

Abbreviations: AraC, cytarabine; ATG, antithymocyte globulin; Bu, busulfan; CSP, cyclosporin; Cy, cyclophosphamide; Flu, fludarabine; GVHD, graft versus host disease; Mel, melphalan; MMF, mycophenolate; MTX, methotrexate; Px, prophylaxis; TAC, tacrolimus; TBI, total body irradiation.

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