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Immunotherapeutic options for Epstein–Barr virus-associated lymphoproliferative disease following transplantation

Donald R Shaffer¹, Cliona M Rooney¹, and Stephen Gottschalk^{1,†}

¹ Center for Cell & Gene Therapy, Baylor College of Medicine, 6621 Fannin Street, MC 3 3320, Houston, TX 77030, USA

Abstract

Epstein–Barr virus-associated lymphoproliferative diseases (EBV-LPD) after hematopoietic stem cell transplantation or solid-organ transplantation remain a serious and potentially life-threatening complication. In the last decade, outcomes for EBV-LPD have significantly improved. Key to this success was the development of early detection methods, such as serial measurements of EBV-DNA load in the peripheral blood of transplant recipients. Immunotherapeutic interventions for EBV-LPD include reduction of immunosuppression, CD20 monoclonal antibodies (rituximab) as monotherapy or in conjunction with chemotherapy, and adoptive immunotherapy with EBV-specific T cells. Pre-emptive immunotherapeutic interventions can prevent the development of EBV-LPD. As monotherapy, immunotherapy is effective in inducing remissions of EBV-LPD with low-risk features. For high-risk disease, combining immunotherapy with conventional therapies has led to superior outcomes. Current challenges consist of risk stratifying patients so that patients receive the most efficacious therapy without suffering from unwanted side effects.

Keywords

Epstein–Barr virus; lymphoproliferative disease; monoclonal antibody; rituximab; T-cell therapy; transplantation

An increased incidence of lymphomas in immunosuppressed transplant recipients was first recognized in 1969 and further studies demonstrated that 90% of these lymphoproliferative diseases (LPDs) were positive for Epstein–Barr virus (EBV) [1,2]. EBV-LPD comprises a heterogeneous group of malignancies, ranging from polyclonal hyperplasias to monoclonal, aggressive non-Hodgkin's lymphomas [3]. The development of EBV-LPD is linked to a deficient EBV-specific cellular immune response. In hematopoietic stem cell transplant (HSCT) recipients, this is caused by high-dose chemotherapy and/or radiation administered as part of the conditioning regimen, T-cell depletion and additional immunosuppression to prevent graft-versus-host disease (GvHD), and in solid-organ transplant (SOT) recipients by immunosuppression administered to prevent graft rejection [4–6]. This article reviews the use of immunotherapeutic intervention for the prevention and treatment of EBV-LPD and summarizes potential strategies to improve current approaches.

[†]Author for correspondence: Tel.: +1 832 824 4179, Fax: +1 832 825 4732, smg@bcm.edu.

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Pathogenesis of EBV-LPD

Epstein–Barr virus is a ubiquitous latent gammaherpes virus infecting more than 90% of the world's population [7,8]. Primary infection usually occurs through the oropharynx, where mucosal epithelial cells and/or B cells become productively infected. During primary infection, EBV establishes lifelong latency in the memory B-cell compartment and the number of latently infected cells remains stable over years at an estimated $1\text{--}50$ cells per 1×10^6 B cells in peripheral circulation [7]. Latently infected cells traffic from blood to the oropharyngeal lymphoid tissue where it is thought that periodic reactivation of EBV into the lytic cycle leads to shedding of virus and infection of new B cells, perpetuating the infection [9]. During acute infection, healthy individuals mount a vigorous humoral and cellular immune response. While antibodies to the viral membrane proteins neutralize viral infectivity, the cellular immune response is required for controlling primary and latent EBV infected cells [10,11].

Epstein–Barr virus poses little threat to the vast majority of immune-competent adults and children, where it exists as a harmless passenger. However, in patients with congenital or acquired immune deficiencies as well as a small minority of otherwise healthy individuals, EBV can cause life-threatening illnesses. In fact, the virus was first isolated in 1964 from 'African lymphoma' (Burkitt's) tumor specimens and has since been associated with a heterogeneous group of malignancies [12–14]. All EBV-associated malignancies involve the virus' latent cycle and EBV-LPD is most often associated with the type III latency program. Type III latency is characterized by expression of all EBV latency proteins, including EBV nuclear antigens (EBNAs) 1, 2, 3A, 3B, 3C, LP, latent membrane protein (LMP)1, LMP2A and LMP2B [7]. In addition, small nonpoly-adenylated viral RNAs (termed Epstein–Barr-encoded RNA-1 and -2), the BamHI-A rightward transcripts (BARTS), and EBV-derived microRNAs are expressed [7,15]. B cells infected *in vitro* with EBV to generate lymphoblastoid cell lines (LCLs) also display a type III latency pattern and have been essential for the generation of EBV-specific cytotoxic T cells (CTLs) for the prophylaxis and treatment of EBV-LPD [16,17].

The importance of T-cell dysfunction in the pathogenesis of EBV-LPD is evidenced by the fact that the majority of cases occur within the first year post-transplant, when the recipient is severely immunosuppressed to prevent GvHD or graft rejection. In addition to EBV and a dysfunctional cellular immune system, genetic alterations in B cells have been implicated in the pathogenesis of LPD, including aberrant somatic hypermutation, microsatellite instability, DNA hypermethylation and mutations in genes such as *c-myc*, *N-ras*, *BCL-6* and *p53* [18,19]. EBV-infected naive, memory and atypical post-germinal center B cells may all give rise to LPD, illustrating its complex pathogenesis [20,21]. LPD is classified according to the WHO into 'early' polymorphic and monomorphic lesions [3]. Early lesions consist of plasmacytic hyperplasia, infectious mononucleosis-like lesions and polymorphic LPD, whereas monomorphic LPD usually resembles non-Hodgkin's lymphomas with diffuse large B-cell lymphomas being most common [22].

Incidence & risk factors

The incidence of EBV-LPD after SOT varies from 1 to 20% depending on the type of organ transplant, with the highest risk after small bowel transplant, followed in descending order by lung, heart, liver and kidney transplant [6,23]. Extensive and prolonged immunosuppression and/or being EBV seronegative at the time of transplant are the two major risk factors for developing LPD after SOT. The incidence of LPD is highest within the first 2 years; however, 10–20% of cases occur more than 10 years post-SOT [22,24].

After allogeneic HSCT, the incidence of LPD varies with the transplant regimen and in some settings may be as high as 40% [25]. More than 80% of LPDs occur within the first year post-HSCT, with a peak incidence in the first 2 and 3 months. The most important risk factor is the level of T-cell depletion of the donor cells, others include the use of stem cells from a HLA-mismatched family member, intensive immunosuppression and an underlying diagnosis of primary immunodeficiency [25]. Thus, in recipients of unmodified stem cell products, who receive GvHD prophylaxis without T-cell-depleting antibodies, the residual EBV-specific T cells in the stem cell product are usually adequate to control EBV reactivation, whereas patients who receive T-cell depleted products or *in vivo* T-cell-depletion with antibodies have an increased risk since the critical balance between EBV-infected B cells and EBV-specific T cells is perturbed. The notion of a critical balance in preventing malignant outgrowth is best exemplified by the finding that the incidence of LPD is significantly lower (<2%) when patients receive alemtuzumab, a CD52 monoclonal antibody, which depletes B and T cells [26,27]. The risk of developing LPD after allogeneic umbilical cord blood transplantation (UCBT) is also less than 2%, but may increase when antithymocyte globulin (ATG) is used in nonmyeloablative conditioning regimens or when T-cell suppressive therapy for GvHD is used [28,29]. LPD following autologous HSCT is extremely rare, unless patients receive T-cell-depleting antibodies or are heavily pretreated. For example, two of 56 patients developed LPD when CD34-selected stem cell products and ATG were used for the treatment of severe autoimmune disease [30]. Disturbing the balance of B and T cells with ATG in patients with autoimmune disease might be the major contributing factor, since these patients already have an increased incidence of EBV-driven lymphoproliferative disease [31,32]. In addition, five of 156 patients developed LPD after receiving high-dose chemotherapy and an autologous CD34-selected stem cell transplant for high-risk pediatric malignancies [33]. All patients who developed LPD had high-risk neuroblastoma as an underlying malignancy and received dose-intense therapy prior to transplant.

Identifying patients at high risk of developing EBV-LPD

Early diagnosis and treatment of LPD leads to better outcomes [22,24,34]. LPD may present with a diverse spectrum of clinical symptoms and signs, underscoring the need for a high index of suspicion in making the diagnosis. To identify patients at high risk of developing EBV-LPD, PCR-based assays to monitor EBV-DNA load in whole blood, peripheral cells or serum/plasma of HSCT and SOT patients are now routinely used in the clinic [35,36]. While initial studies performed in HSCT recipients receiving T-cell-depleted grafts suggested that a rising EBV-DNA load was highly predictive for the development of LPD, studies performed on recipients receiving unmanipulated grafts suggested elevated EBV-DNA loads were less predictive, with one study reporting only 10% of patients with increased EBV-DNA developing LPD [36–39].

Discrepancies in the literature with regards to EBV-DNA load measurements have to be attributed to the lack of a WHO standard for monitoring EBV-DNA load. Thus, centers use different PCR-based assays and starting material (whole blood, peripheral cell or serum/plasma) making comparison across centers difficult. What constitutes a ‘high EBV load’ is in part assay-specific; however, serial monitoring of EBV-DNA can be useful to distinguish patients with a chronic, stable elevated EBV-DNA load from those with a continuously increasing load indicative of impending EBV-LPD. Further analysis of ‘chronic high-load carriers’ has revealed several distinct patterns of EBV latent gene expression in memory B cells, with a type III latency conferring the highest risk of EBV-LPD development [40]. These assays are, however, not routinely available. Thus, an elevated EBV-DNA load can lead to early diagnosis of EBV-LPD; however, other factors such as clinical symptoms and signs, and results of diagnostic imaging studies must be taken into account before

initiating therapy. Besides EBV-DNA load, determining the frequency of EBV-specific T cells, the functionality of T cells, or polymorphisms in the promoter regions of cytokines in patients with high EBV-DNA load might assist in identifying high-risk patients [41–45].

Immunotherapy of post-transplant lymphoproliferative disorder in hematopoietic stem cell transplant recipients

A variety of treatment approaches have been explored for EBV-LPD primarily focused on boosting the immune response to EBV and restoring the critical balance between EBV-specific T cells and EBV-infected B cells. In SOT recipients, simply reducing or withdrawing immunosuppressive therapy can tip the balance in favor of the patient's immune system allowing endogenous control of developing LPD. However, this strategy proves largely ineffective in HSCT recipients owing to the complete ablation of the immune system and carries the risk of inducing GvHD. The most successful forms of immunotherapy for EBV-LPD include the use of B-cell monoclonal antibodies and the adoptive transfer of donor-derived T cells.

Therapy with B-cell monoclonal antibodies

The first antibodies used to treat EBV-LPD in HSCT patients were murine monoclonal antibodies directed against the B-cell antigens CD21 and CD24. These antibodies were efficacious producing complete responses in 16 out of 28 (57%) HSCT patients with EBV-LPD; however, they are no longer commercially available [46]. Subsequently, rituximab, a humanized monoclonal antibody to CD20, was approved to treat low-grade non-Hodgkin's lymphoma. Shortly thereafter, numerous case reports and eventually larger clinical studies demonstrated rituximab's effectiveness in preventing and treating EBV-LPD [47–53]. An early retrospective analysis of 26 SOT and six HSCT patients treated with rituximab for LPD found an overall response rate of 69% with 20 patients having complete responses, including five out of six HSCT patients [54]. Styczynski *et al.* conducted an extensive review of literature, which included articles and abstracts published between 1999 and 2008: rituximab as pre-emptive therapy prevented the development of EBV-LPD in 89.7% of 341 HSCT recipients, while as standard therapy was associated with a response rate of 63% in 126 HSCT patients [55]. However, response rates varied widely, probably reflecting heterogeneity in patient populations and the fact that early diagnosis and treatment leads to better outcomes. While rituximab has an excellent safety record, it causes profound B-cell depletion for 6–8 months with unknown long-term side effects in patients who receive continuous immunosuppression, such as SOT recipients [56]. Thus, its use as preemptive therapy should be limited to situations in which clinical symptoms and EBV-DNA load indicate a strong likelihood of lymphoma development.

Cellular immunotherapy

Donor lymphocyte infusions (DLIs) have been used successfully to treat EBV-LPD post-HSCT [57,58]. However, its use is limited by the high risk of inducing potentially fatal GvHD. One strategy to overcome this limitation involves transducing donor lymphocytes with a suicide gene so that they can be eradicated should GvHD develop. The herpes simplex virus thymidine kinase gene (*HSV-Tk*), which renders cells sensitive to ganciclovir (GCV), has been used as a suicide gene in several clinical studies [59,60].

Recently, Ciceri *et al.* reported that out of 28 patients receiving *HSV-Tk*-transduced donor lymphocytes, ten developed GvHD, which could be successfully controlled by the administration of GCV [61]. Drawbacks of this approach are the inherent immunogenicity of *HSV-Tk* and the use of nucleoside analogs for inducing T-cell killing, which precludes their use as antiviral agents. Therefore, alternative means of inducing cell death are being

investigated, including the use of inducible Fas or caspase suicide genes in combination with chemical inducers of dimerization, or the ectopic expression of CD20 on donor lymphocytes in combination with rituximab [62–64].

An effective strategy for the prophylaxis and treatment of LPD, circumventing the problem of DLI-induced GvHD, is the infusion of poly-clonal EBV-specific donor CTL (EBV-specific CTL). Our group has treated 101 HSCT recipients prophylactically with EBV-specific CTLs. None developed post-transplant LPD over 15 years of follow-up, compared with five out of 42 (11%) patients enrolled on the same transplantation protocol who did not receive EBV-specific CTLs [16,17,65,66]. Importantly, CTL infusions were safe and not associated with *de novo* GvHD. In 13 patients treated with EBV-specific CTL for biopsy-proven or probable LPD, 11 achieved complete remission with no recurrence. Of the two nonresponders, one patient had extensive CNS disease and died 8 days after CTL infusion. Analysis of the second patient who progressed after CTL infusion revealed a deletion in the EBV protein EBNA 3B, in which two of the dominant epitopes recognized by the infused CTL product were deleted, highlighting a rare and previously unseen mechanism of immune escape to EBV-specific CTL therapy [67]. Thus, EBV-specific CTL therapy has proven to be safe and effective for the prevention and treatment of LPD. The safety and efficacy of donor-derived EBV-specific CTL has been confirmed by other investigators [68,69].

For more aggressive, advanced-stage EBV-LPD, genetic modification of EBV-specific CTLs might provide one strategy to enhance their efficacy [70–72]. Options include the expression of chimeric antigen receptor specific for targeting non-EBV antigens expressed on lymphomas such as CD19 or CD30 [73,74], or rendering CTLs resistant to inhibitory factors secreted by lymphomas such as TGF- β [75].

Drawbacks of EBV-specific CTL therapy are the specialized facilities and time required (3–4 months) for CTL production. The use of banked, allogeneic EBV-specific CTL for ‘off-the-shelf’ therapy is one strategy to overcome this limitation (see below) [76–78]. Successful strategies to reduce the production time of EBV-specific CTLs include the use of EBV-peptide-stimulated donor blood cells combined with IFN- γ capture to select EBV-specific CTLs and the use of dendritic cells nucleofected with DNA plasmids encoding immunodominant EBV antigens to rapidly generate EBV-specific CTL [79,80].

Moosmann *et al.* treated six patients with EBV-specific CTL activated with EBV-derived peptides, and observed three complete responses in patients with early EBV-LPD, whereas three patients with late-stage disease progressed after therapy [79]. While these initial results are encouraging, all responding patients in this study received additional therapies including rituximab, making it difficult to ascribe the anti-LPD effects to CTL alone. Thus, further studies are needed to definitively assess the efficacy and safety of rapidly generated EBV-specific CTL.

Immunotherapy of EBV-LPD in solid-organ transplant recipients

Reducing immunosuppression is considered the first-line therapy of early EBV-LPD post-SOT. Second-line immunotherapeutic options include rituximab alone or in combination with chemotherapy. If available, adoptive transfer of EBV-specific CTL should be reserved for patients, who fail front-line therapies.

Reduction of immunosuppression

Reduction of immunosuppression (RI) can result in the complete resolution of EBV-LPD. Response rates to RI vary from 7 to 63%, most likely reflecting better outcomes with polyclonal disease, and early diagnosis and treatment [5,81,82]. At present, it is unclear by how

much to reduce the immunosuppression and many centers employ a stepwise approach with an initial reduction of 50%. Since RI may be associated with allograft rejection, graft function must be monitored closely especially for heart, lung and liver allografts for which no effective ‘back-up therapy’ (e.g., hemodialysis for renal allografts) is available.

Therapy with B-cell monoclonal antibodies

As for EBV-LPD in HSCT recipients, the use of rituximab had a major impact on current treatment regimens. Therapy of EBV-LPD with rituximab resulted in response rates of 50–100% in SOT recipients, most likely reflecting heterogeneity in the treated patient populations [83–90]. In a recent multicenter analysis of 80 patients with EBV-LPD post-SOT, patients who received rituximab-based therapy had a 3-year progression-free survival of 70% compared with 21% for patients treated without rituximab [24]. In total, 30 out of 59 patients treated with rituximab also received chemotherapy, most of them having bulky disease and a high International Prognostic Index (IPI). At present, it is unclear for which group of patients rituximab monotherapy is sufficient. Retrospective studies have identified risk factors including extralymphatic disease, high lactate dehydrogenase, low albumin and poor performance status; however, prospective studies are required to validate individual risk factors [24,22]. In summary, rituximab has led to a dramatic improvement in outcome of EBV-LPD. However, rituximab does not restore the cellular immune response to EBV, which may be crucial for the long-term control of EBV-mediated B-cell proliferation. EBV-infected B cells may therefore increase with B-cell recovery and EBV-LPD may recur. However, the incidence of late recurrences post-rituximab is currently unknown. While rare, the recurrence of CD20-negative lymphomas with the use of rituximab has been reported [91,92].

Cellular immunotherapy

The success of the adoptive transfer for the prophylaxis and treatment of EBV-specific CTLs in HSCT recipients has led to evaluation of this approach in SOT recipients who are at risk of developing EBV-LPD. Infusions of autologous EBV-specific CTLs into SOT patients with elevated EBV-DNA load have demonstrated that CTL did not cause graft rejection, increased EBV-specific cellular immune responses and had antiviral and anti-tumor effects [43,93–96].

However, in contrast to HSCT recipients, the infused EBV-specific CTLs persisted only transiently, indicating that CTLs do not persist in the chronic immunosuppressive environment of SOT recipients. Thus, genetically modifying CTLs to render them resistant to immunosuppressive drugs, such as FK506, might improve current CTL therapies in SOT recipients [97,98].

As for HSCT recipients, the use of EBV-specific CTL in SOT recipients is limited by the time needed to generate CTL products. While rapid CTL production protocols are being developed, the use of ‘banked’ allogeneic EBV-specific CTL, which are readily available, is actively being explored [76–78]. In one multi-center clinical trial, 31 SOT and two HSCT recipients with EBV-LPD, who had failed conventional therapies, received allogeneic EBV-specific CTL. CTL infusions were well tolerated with no evidence of graft rejection. The overall response rate was 52% at 6 months, including 14 patients with a complete response [78]. The degree of HLA matching between patients and the infused CTL product correlated with outcome; however, clinical responses were observed with significant HLA-disparities [78]. A detailed analysis of the specificity of the infused, allogeneic CTLs revealed that CTL might also induce nonspecific inflammatory responses, which contributed to the observed tumor regressions [99]. As for the adoptive transfer of autologous EBV-specific CTL, allogeneic CTL persistence in patients’ peripheral blood was limited.

Other immunotherapeutic options

IFN- α , a proinflammatory and antiviral cytokine, has been used as an immunotherapeutic intervention for EBV-LPD in the pre-rituximab era. While IFN- α therapy can induce regression of polyclonal EBV-LPD, it is associated with a high risk of graft rejection [81,100]. IL-6, a pleiotropic cytokine, is an autocrine growth factor for the proliferation of EBV-infected B cells. In a multi-center Phase I/II clinical trial 12 SOT recipients with EBV-LPD were treated with IL-6 antibodies with five complete and three partial remissions [101]. While a US FDA-approved IL-6 antibody is currently not available, an IL-6 receptor antibody, tocilizumab, was recently approved for the treatment of rheumatoid arthritis. Since tocilizumab may be associated with the reactivation of chronic active EBV infections [102], studies are needed to define its role in the treatment of LPD.

Conclusion

After transplantation, EBV-LPD remains a life-threatening disease. Early diagnosis and treatment is key to assure good outcomes. There is convincing evidence that pre-emptive immunotherapeutic interventions can prevent the development of EBV-LPD. As treatment, immunotherapy is effective in inducing remissions of EBV-LPD with low-risk features. For high-risk disease, combining immunotherapy with conventional therapies has led to superior outcomes over conventional therapies alone. In addition, while monoclonal antibodies are readily available, CTL therapies are currently limited to a few centers. Initial multicenter clinical studies with 'banked CTL' have produced encouraging results, indicating that this therapeutic option might become more readily available in the future. Finally, genetic modification of CTL holds the promise to improve their therapeutic efficacy.

Future perspective

Current challenges consist of risk stratifying EBV-LPD patients so that patients receive the most efficacious therapy without suffering from unwanted side effects. To achieve this, we need better algorithms on how to identify patients with imminent, early LPD, consensus on definition of LPD and standardized intervention approaches, which are evaluated in multicenter clinical trials. As a first step towards this goal, development of a WHO standard for EBV-DNA load measurement is critical, since it would allow the comparison of current screening strategies between centers. Finally, multicenter clinical trials are needed to define the role of cellular therapies for EBV-LPD.

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▪ of interest

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