IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A Review On Epstein-Barr Virus (Ebv)

[1]Mr. Kangare saurabh Dadasaheb*, [2]Mr.Ajit B. Tuwar ,[3]Dr. Megha T. Salve
[1]Shivajirao Pawar College of Pharmacy, Pachegaon, Tq. Newasa, Dist.Ahmednagar, Maharashtra,India.
[2]Department of Pharmacy, Pachegaon, Ahmednagar-413725

Abstract:
Epstein-Barr virus (EBV) is a herpesvirus that affects the majority of people worldwide. The virus can develop a long-term latent infection in the host's B lymphocytes. In immunosuppressed (e.g. post-transplant) patients, the disease can reactivate, and the most dangerous is after hematopoietic stem cell transplantation (HSCT), postlymphoproliferative disease (PTLD), which is increasingly the case. Several risk factors, including age, decreased immunity, EBV serologic incompatibility, and cytomegalovirus (CMV) reactivation, are associated with the development of PTLD. There are few clinical studies on PTLD and no clinical consensus, making the management of PTLD difficult. Although initial therapy includes weekly rituximab administration, there is no consensus on the treatment of rituximab-resistant PTLD. There are clinical studies evaluating the role of EBV-specific cytotoxic T lymphocytes (CTL) and newer drugs such as bortezomib, lenalidomide, everolimus, panobinostat, and brentuximab. This article aims to investigate the EBV-PTLD association in HSCT recipients, detailing clinical outcomes, risk factors, care, and treatment, thus highlighting the mystery that must be created to establish an appropriate treatment plan for all at-risk patients.

Keywords: Epstein- Barr virus(EBV),Epidemiology,Pthogenesis, Treatment.

INTRODUCTION

Epstein-Barr virus (EBV) is a herpesvirus that affects 50% to 89% of children and more than 90% of adults worldwide [1, 2]. Human Herpesviruses Epstein-Barr virus (EBV or human herpesvirus 4, HHV-4) is one of the most common herpesviruses, infecting 95% of adults. Initial EBV infection usually occurs in childhood and is often asymptomatic. However, EBV infection in adolescence and early adulthood can cause mononucleosis in 35% to 50% of patients. Symptoms of mononucleosis (fatigue, fever, sore throat, swollen lymph nodes in the neck, spleen enlargement, liver swelling, rash) usually resolve within 1 day for 2 months, although in young people, symptoms of fatigue appear after resolution of pleocytosis. The disease is followed by a 13%, 7%, and 4% reduction at 6, 12, and 24 months, respectively [3]. A fixed latency period is established after the onset of infection. However, EBV can still cause serious diseases of the immune system and many life-threatening diseases of lymphoid and epithelial cell origin (congenital, in the setting of HIV infection or due to mutations and autoimmune diseases due to use of immunomodulatory drugs). EBV has been shown to play a role in the development of B-cell malignancies such as Burkitt lymphoma and other non-Hodgkin lymphomas, Hodgkin lymphoma, central nervous system lymphoma and post-transplant lymphoproliferative disorder (PTLD), AIDS-related lymphomas, as well as natural killer (NK) and T-cell lymphomas [4,5]

Pathogenesis

This virus prefers to infect B lymphocytes through its target receptor CD21, where EBV remains in an asymptomatic latent state throughout the life of the host, but EBV-associated lymphoma can develop in conditions of good immune resistance. In immunocompromised individuals, after the initial infection with infectious mononucleosis, the disease is controlled by EBV-specific cytotoxic T lymphocyte (CTL) activity [6]. Here, the virus circulates its genome, restricts the viral load and establishes a long latency period [2, 7]. The latent virus proteome can direct memory B cells to the central nervous system and allow EBV in the peripheral blood and reticuloendothelial system [8]. This concept becomes important when considering antiviral drugs that frequently target EBV during infection, such as ganciclovir. Drugs such as ganciclovir require phosphorylation of viral kinases that are not usually expressed and therefore not used during latent infection [9]. Host escape. For example, chronic exposure of an individual's immune system to EBV latent proteins such as latent membrane protein (LMP) activates the JAK/STAT pathway in infected B cells, leading to expression of the co-inhibitory receptor PD-L1 [10], while T cells become inactivated when they bind to the PD-1 receptor, leading to errors and exhaustion of immunity to EBV [10]. In addition, the virus can downregulate MHC class I and class II proteins to avoid harming the body [11]. Although HLA-class I downregulation allows EBV to evade the host immune system, it also makes it more susceptible to natural killer (NK) cells [12]. One study investigated this issue by examining the NK response of three donor peripheral blood mononuclear cells (PBMCs) to Ataka cells (a Burkitt lymphoma cell line latently infected with EBV) and EBV-negative Ataka cells after incubation [13]. After incubation of donor PBMC with EBV-positive Ataka cells, the number of NK cells increased significantly (p value < 0.001), indicating the role of NK cells in maintaining EBV-positive cells [13]. Although rare, EBV is highly contagious, but it is possible for individuals to develop EBV-associated lymphoma. This is often modified by race, geography, genetics, immune system and infection [14]. In immunocompromised individuals, T lymphocyte immunity is compromised and EBV viremia delays the lifespan of B lymphocytes causing lymphoma/AKT/mTOR, BCL2, leading to increased transcription (e.g. BCL6, MYC, NF-kB, PI3K) and immunoglobulin switching allowing progression from early polymorphic lymphoma to more advanced monoclonal [15–23]. Although >90% of EBV-PTLD patients in organ transplant (SOT) recipients are hosts, the majority of EBV-PTLD after HSCT are donors [24]. When immunodeficiency occurs after HSCT, the graft creates a unique immunocompromised environment, allowing donor-derived EBV-infected B lymphocytes to invade the immunocompromised host and cause lifelong problems such as PTLD [25]. EBV-positive PTLD is usually reported in the first year after transplantation, with the majority occurring in the first 6 months [26]. EBV-negative PTLD, on the other hand, occurs more than 5 years after transplantation, with some cases occurring as late as 10 years after transplantation. At the genomic level, there appears to be an important difference between these two entities: EBV-negative cases share genomic features with diffuse large B-cell lymphoma in immunocompetent individuals, whereas EBV-positive cases do not [12 , 26]. This is reflected in the greater number and complexity of molecular abnormalities in EBV-negative PTLD compared to EBV-positive PTLD [12, 26]. Therefore, EBV-positive PTLD occurs in the early immunodeficiency period after transplantation due to low molecular/genetic alterations. Therefore, EBV-negative PTLD can be compared to non-transplantation site large B-cell lymphoma. Despite the differences between the two entities, they appear to respond similarly to treatment and therefore EBV status does not appear to have a prognostic value [26].

EBV-PTLD epidemiology

The incidence of EBV-PTLD after allogeneic HSCT ranges from 0.5% to 17% [25–28]. The incidence of PTLD is increasing due to the increasing number of transplants, aging population and age of the recipient, new vaccines, increased demand for haploidentical HSCT, and increased awareness of the disease [29]. However, this has led to improvements in diagnostic tools [30]. EBV can infect cells other than hematopoietic cells, causing various conditions such as hepatitis, gastroenteritis, pneumonia, nephritis, and encephalitis. According to the 2016 classification of the World Health Organization (WHO), PTLD can be divided into: plasmacytosis, infectious mononucleosis, follicular hyperplasia, pleomorphic, monomorphic, and classical Hodgkin lymphoma [32]. PTLD can occur at any time after transplantation, even up to 10 years after transplantation [33]. However, the majority of cases (60%) occur within the first year of transplantation [34, 35]. This is consistent with previous studies showing that the risk of developing EBV-PTLD is highest in the first year after HSCT, with 83% of patients presenting at this time and most occurring within the first 6 months after transplantation [23]. As previously mentioned, early-stage PTLD appears to be dependent on EBV, whereas late-stage PTLD is not

[4]. The occurrence of PTLD alone reduces patient survival from 62% to 20% [36]. A previous mortality analysis in PTLD patients in over 200 transplant centers showed that mortality due to PTLD was as high as 84% [37]. However, rigorous use of diagnostic and therapeutic strategies, such as monitoring for EBV DNAemia and early treatment with new drugs such as rituximab, has successfully reduced mortality due to PTLD from 84% before 2000 to 30% in 2013 [37 -39]. To establish the diagnosis of EBV-PTLD, the following two conditions must be met: (a) the lymphocyte proliferation process destroys the cellular structure, (b) the presence of monoclonal or oligoclonal viral markers, and (c) EBV infection is determined by detectable viral nucleic acid or protein [32]. When PTLD is suspected based on clinical signs or elevated peripheral blood EBV DNA levels, tissue biopsy is required to confirm the diagnosis of PTLD and distinguish it from other diseases [40]. These samples are usually obtained by hollow needle or partial resection from the central or fluorodeoxyglucose (FDG)-rich region of the tumor [40]. Samples should be tested for clonal immunoglobulin heavy or light chains, T cell receptor gene rearrangements, and EBV-LMP immunostaining [40]. It is important to note that EBV nucleic acid in serum alone is not sufficient to diagnose EBV-PTLD [38]. When EBV-PTLD is diagnosed, clinical evaluation should be performed to assess disease and pathology in the spinal cord using PET-CT, bone marrow biopsy, cerebrospinal fluid analysis, and brain magnetic resonance imaging [40]. These include older age, noncompliance with rituximab therapy, delayed immune response resulting in thrombocytopenia (<50 × 109/L) and leukopenia (<0.5 × 109/L) at diagnosis, and extranodal malignant disease at the time of PTLD diagnosis. GVHD ≧ grade II [39, 41]. Elevated lactate dehydrogenase (LDH) levels have previously been identified as a risk factor in PTLD after SOT, but there are concerns about its validity in PTLD after HSCT [42]. However, it is associated with clinical manifestations of PTLD [33]. Baseline patient characteristics such as advanced age, especially over 50 years, history of splenectomy, and other variables described below provide good chances of curing PTLD. The risk of developing PTLD increases as the patient accumulates risk factors [36]. Ulin et al. [36] studied 1021 patients, 4% of whom developed PTLD, and found that RIC use was an independent risk factor for the development of EBV-PTLD (hazard ratio (HR) 3.25; p-value 0.002). The effect of RIC on PTLD may be explained by EBV tropism for B lymphocytes. After RIC, EBV-infected lymphocytes have time to spare for transplantation in the absence of the usual restriction of EBV-specific T lymphocytes [36]. In addition, several studies have shown that T cell reconstitution is delayed after RIC compared with myeloablative conditioning (MAC) [43, 44]. [36] found that HLA-mismatched graft recipients had a higher risk of developing EBV-PTLD compared with HLA-identical graft recipients (HR 5.89, p-value <0.001). Another study found that HSCT recipients who received two or more HLA-mismatched donors (relative risk (RR), 3.1) or unrelated affected individuals (RR 4.2) had a higher risk of HSCT than those who received the same donor or multiple transplant recipients. 1 HLA mismatch is associated with developing PTLD (RR 1.8). Over the years, the results of various studies regarding the association between EBV-PTLD and specific HLA class I antigens have been conflicting. This conflict can be addressed in a variety of ways [45-49,23].

EBV donor/recipient serology mismatch: As expected, EBV serology mismatch between donor and recipient is another important risk factor for EBV reactivation and development of PTLD in the recipient. This combination has been found to be a significant risk factor for the development of PTLD in HSCT recipients, with an HR of 4.97 (p value <0.001) [36]. Cyclophosphamide is increasingly used for the prevention of post-transplant GVHD in allogeneic transplantation. Initially, cyclophosphamide, like many other drugs shown to be effective in preventing GVHD, was thought to increase the incidence of post-transplant EBV-PTLD. A retrospective analysis of 785 allogeneic HSCT performed with cyclophosphamide after transplantation found zero cases of EBVPTLD [52]. -Another independent risk factor for PTLD (HR 2.65; p-value 0.006) [33]. Other studies also agree with this result [53, 54]. This may be due to a specific immune response resulting from proinflammatory cytokines released in GVHD in addition to the protective immune system [37]. The problem is that there is no medical approval in the United States or Europe. The impact on treatment is due to changes in patient response to treatment, limitations and toxicities associated with current therapy, lack of EMA and FDA approved therapy, lack of international interest and, importantly, lack of randomized trials [29, 55]. Response to RIS varies from 0% to 73% but is not transient, as stable responses occur in <10–20% of patients [95–63]. There are two specific problems when dealing with HSCT patients: (a) the median response time after RIS is very long, approximately 3–5 weeks, and (b) an increased risk of failure/rejection after RIS[35]

Tuximab results:

Rituximab is a monoclonal anti-CD20 antibody proven in non-destructive PTLD, polymorphic PTLD, and monomorphic diffuse large B-cell lymphoma resistant to RIS as the standard treatment for patients with PTLD [29].

Rituximab is effective in EBV-PTLD not only because it targets CD20+ tumor cells, but also because of its effect on B-cell depletion, which changes the ratio of EBV-infected B lymphocytes to EBV-T lymphocytes, particularly favoring the antibiotic/antibiotic tumor response [64]. Rituximab as first-line monotherapy has reported response rates of approximately 60–65% and as high as 80% [64–66]. The 20% treatment failure rate makes the use of rituximab as monotherapy inadequate. Therefore, rituximab is often combined with RIS or cellular immunotherapy (e.g. EBV-CTL). Approximately 44–79% of patients respond to rituximab in combination with RIS therapy, with a complete response rate of 20–55% [66–72]. Limitations in the management of patients with relapsed or rituximab-refractory PTLD are the lack of consensus and consensus. Therefore, survival of patients with relapsed or rituximab-refractory disease is poor, with only 28% of HSCT patients and 36% of SOT patients expected to survive after 1 year [36, 71].

Antiviral therapy:

During initial infection, EBV encodes thymidine kinase, an enzyme that converts nucleoside analogs to the monophosphate form; this enzyme is then converted by cellular enzymes to the triphosphate that targets viral DNA polymerase, inhibiting viral replication and thus inducing apoptosis. Thus, antiviral drugs such as ganciclovir have an effect on EBV infection during in vitro lytic infection. EBV-infected cells transform B cells that lack lytic viral activity and are therefore insensitive to in vitro antiviral therapy [73]. Furthermore, as previously mentioned, during latent infection, EBV cyclizes and inhibits the expression of specific proteins such as thymidine kinase [74]. This makes EBV less susceptible to antibodies during latency. A meta-analysis investigated the effect of antiviral therapy after SOT on the incidence of PTLD in patients with EBV serology-discordant liver [74]. No effect was seen regardless of the type of mutation, type of vaccine, duration of vaccination or age of the patient [74]. Such results may be relevant to the situation after HSCT transplantation because the proliferation of EBV-infected B cells behaves similarly regardless of whether EBV is transmitted as a donor or a recipient.

Conclusion

EBV-PTLD is a serious complication that can occur in severely immunocompromised HSCT recipients. Although this association impacts survival, due to the small number of clinical trials and the rarity of the disease, comparative data to evaluate treatment strategies are lacking, and there is no clear consensus regarding their use in the treatment of PTLD in transplant recipients. Studies have identified risk factors for the development of PTLD, including HLA incompatibility, EBV serology incompatibility, development of GVHD, non-MAC RIC, and T-cell depletion. Physicians may intervene in patients at high risk of disease based on these risks and patient characteristics. Currently, guidelines support weekly monitoring of EBVDNA and weekly pretreatment with rituximab (1–4 doses) alone or in combination with RIS or CTL when possible. Combination therapy awaits results from clinical trials investigating new technologies or drugs such as “off-the-shelf” CTLs, bortezomib, lenalidomide, everolimus, brentuximab, and panobinostat.

Acknowledgement: The author would like to thank Prof. Babasaheb Chopade sir, Prof. Ajit B. Tuwar sir , Dr. Megha Salve mam, Dr. Abhijeet Shete sir and all persons directly or indirectly involved in the preparation of this article.

REFERENCES:

[1]. Balfour HH Jr., Dunmire SK, Hogquist KA. Infectious mononucleosis. Clin Transl Immunology. 2015;4:e33.

[2]. Cohen JI. Epstein-Barr virus infection. N Engl J Med. 2000;343:481–92.

[3]. Katz, B.Z.; Shiraishi, Y.; Mears, C.J.; Binns, H.J.; Taylor, R. Chronic fatigue syndrome after infectious mononucleosis in adolescents. Pediatrics **2009**, 124, 189–193.

[4]. Cesarman, E. Gammaherpesvirus and lymphoproliferative disorders in immunocompromised patients. Cancer Lett. **2011**, 305, 163–174.

[5]. Cesarman, E. Gammaherpesviruses and lymphoproliferative disorders. Annu. Rev. Pathol. **2014**, 9, 349–372.
[6]. Comoli P, Basso S, Zecca M, Pagliara D, Baldanti F, Bernardo ME, et al. Preemptive therapy of EBV-related lymphoproliferative disease after pediatric haploidentical stem cell transplantation. Am J Transplant. 2007;7:1648–55.
[7]. Yates J, Warren N, Reisman D, Sugden B. A cis-acting element from the Epstein-Barr viral genome that permits stable replication
of recombinant plasmids in latently infected cells. Proc Natl Acad Sci USA. 1984;81:3806–10.
[8]. Shannon-Lowe C, Rickinson AB, Bell AI. Epstein-Barr virusassociated lymphomas. Philos Trans R Soc Lond B Biol Sci.2017;372:1732.
[9]. Kalinova L, Indrakova J, Bachleda P. Post-transplant lymphoproliferative disorder. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2009;153:251–7.
[10]. Ferreiro JF, Morscio J, Dierickx D, Vandenberghe P, Gheysens O, Verhoef G, et al. EBV-positive and EBV-negative posttransplant diffuse large B cell lymphomas have distinct genomic and transcriptomic features. Am J Transplant. 2016;16:414–25.
[11]. Quinn LL, Williams LR, White C, Forrest C, Zuo J, Rowe M. The missing link in epstein-barr virus immune evasion: the BDLF3 gene induces ubiquitination and downregulation of major histocompatibility complex class I (MHC-I) and MHC-II. J Virol. 2016;90:356–67.
[12]. Ressing ME, Keating SE, van Leeuwen D, Koppers-Lalic D, Pappworth IY, Wiertz EJ, et al. Impaired transporter associated with antigen processing-dependent peptide transport during productive EBV infection. J Immunol. 2005;174:6829–38.
[13]. Djaoud Z, Guethlein LA, Horowitz A, Azzi T, Nemat-Gorgani N, Olive D, et al. Two alternate strategies for innate immunity to Epstein-Barr virus: One using NK cells and the other NK cells and gammadelta T cells. J Exp Med. 2017;214:1827–41.
[14]. Kanakry JA, Ambinder RF. EBV-related lymphomas: new approaches to treatment. Curr Treat Options Oncol.2013;14:224–36.
[15]. Henderson S, Rowe M, Gregory C, Croom-Carter D, Wang F, Longnecker R, et al. Induction of bcl-2 expression by Epstein-Barr virus latent membrane protein 1 protects infected B cells from programmed cell death. Cell. 1991;65:1107–15.
[16]. Capello D, Rossi D, Gaidano G. Post-transplant lymphoproliferative disorders: molecular basis of disease histogenesis and pathogenesis. Hematol Oncol. 2005;23:61–7.
[17]. Krams SM, Martinez OM. Epstein-Barr virus, rapamycin, and host immune responses. Curr Opin Organ Transplant. 2008;13:563–8.
[18]. Vereide DT, Sugden B. Lymphomas differ in their dependence on Epstein-Barr virus. Blood. 2011;117:1977–85.
[19]. Burns DM, Tierney R, Shannon-Lowe C, Croudace J, Inman C, Abbotts B, et al. Memory B-cell reconstitution following allogeneic hematopoietic stem cell transplantation is an EBVassociated transformation event. Blood. 2015;126:2665–75.
[20]. Friedberg JW, Swinnen L. Post-transplant lymphoproliferative disease in the lymphomas. 2nd ed. Philadelphia, PA, USA: Elsevier; 2006.
[21]. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H et al. WHO classification of tumors of haemotopoietic and lymphoid tissue. 4th ed. Lyon: IARC; 2008.
[22]. Ruf S, Moser O, Wossmann W, Kreyenberg H, Wagner HJ. Examining the origin of posttransplant lymphoproliferative disorder in a patient after a second allogeneic hematopoietic stem cell transplantation for relapsed BCR-ABL positive acute lymphoblastic leukemia. J Pedia Hematol Oncol. 2011;33:50–4.
[23]. Landgren O, Gilbert ES, Rizzo JD, Socie G, Banks PM, Sobocinski KA, et al. Risk factors for lymphoproliferative disorders after allogeneic hematopoietic cell transplantation. Blood. 2009;113:4992–5001.
[24]. Luskin MR, Heil DS, Tan KS, Choi S, Stadtmauer EA, Schuster SJ, et al. The impact of EBV status on characteristics and outcomes of posttransplantation lymphoproliferative disorder. Am J Transplant. 2015;15:2665–73.
[25]. Johansson JE, Remberger M, Lazarevic V, Hallbook H, Wahlin A, Kimby E, et al. Allogeneic haematopoietic stem-cell transplantation with reduced intensity conditioning for advanced stagen

Hodgkin's lymphoma in Sweden: high incidence of post transplant lymphoproliferative disorder. Bone Marrow Transplant. 2011;46:870–5.
[26]. Hou HA, Yao M, Tang JL, Chen YK, Ko BS, Huang SY, et al. Poor outcome in post transplant lymphoproliferative disorder with pulmonary involvement after allogeneic hematopoietic SCT: 13 years' experience in a single institute. Bone Marrow Transplant. 2009;43:315–21.
[27]. Buyck HC, Ball S, Junagade P, Marsh J, Chakrabarti S. Prior immunosuppressive therapy with antithymocyte globulin increases the risk of EBV-related lymphoproliferative disorder following allo-SCT for acquired aplastic anemia. Bone Marrow Transplant. 2009;43:813–6.
[28]. Ocheni S, Kroeger N, Zabelina T, Sobottka I, Ayuk F, Wolschke C, et al. EBV reactivation and post transplant lymphoproliferative disorders following allogeneic SCT. Bone Marrow Transplant. 2008;42:181–6.
[29]. Dierickx D, Habermann TM. Post-transplantation lymphoproliferative disorders in adults. N Engl J Med. 2018;378:549–62.
[30]. Gu B, Chen GH, Wu DP. [Recent advances on diagnosis and therapy of lymphoproliferative disorders after allo-HSCT]. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2014;22:538–42.
[31]. Deeg HJ, Socie G. Malignancies after hematopoietic stem cell transplantation: many questions, some answers. Blood. 1998;91:1833–44.
[32]. Tamaru JI. 2016 revision of the WHO classification of lymphoid neoplasms. Rinsho Ketsueki. 2017;58:2188–93.
[33]. Rasche L, Kapp M, Einsele H, Mielke S. EBV-induced post transplant lymphoproliferative disorders: a persisting challenge in allogeneic hematopoetic SCT. Bone Marrow Transplant. 2014;49:163–7.
[34]. Zimmermann H, Trappe RU. Therapeutic options in posttransplant lymphoproliferative disorders. Ther Adv Hematol. 2011;2:393–407.
[35]. Al-Mansour Z, Nelson BP, Evens AM. Post-transplant lymphoproliferative disease (PTLD): risk factors, diagnosis, and current treatment strategies. Curr Hematol Malig Rep. 2013;8:173–83.
[36]. Uhlin M, Wikell H, Sundin M, Blennow O, Maeurer M, Ringden O, et al. Risk factors for Epstein-Barr virus-related posttransplant lymphoproliferative disease after allogeneic hematopoietic stem cell transplantation. Haematologica. 2014;99:346–52.
[37]. Curtis RE, Travis LB, Rowlings PA, Socie G, Kingma DW, Banks PM, et al. Risk of lymphoproliferative disorders after bone marrow transplantation: a multi-institutional study. Blood. 1999;94:2208–16.
[38]. Styczynski J, Reusser P, Einsele H, de la Camara R, Cordonnier C, Ward KN, et al. Management of HSV, VZV and EBV infections in patients with hematological malignancies and after SCT: guidelines from the Second European Conference on Infections in Leukemia. Bone Marrow Transplant. 2009;43:757–70.
[39]. Styczynski J, Gil L, Tridello G, Ljungman P, Donnelly JP, vander Velden W, et al. Response to rituximab-based therapy and risk factor analysis in Epstein Barr Virus-related lymphoproliferative disorder after hematopoietic stem cell transplant in children and adults: a study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Clin Infect Dis. 2013;57:794–802.
[40]. DeStefano CB, Desai SH, Shenoy AG, Catlett JP Management of post-transplant lymphoproliferative disorders. Br J Haematol. 2018;182:330–343.
[41]. Garcia-Cadenas I, Yanez L, Jarque I, Martino R, Perez-Simon JA, Valcarcel D, et al. Frequency, characteristics and outcome of PTLD after allo-SCT: a multicenter study from the Spanish group of blood and marrow transplantation (GETH). Eur J Haematol. 2019;00:1–7.
[42]. Evens AM, David KA, Helenowski I, Nelson B, Kaufman D, Kircher SM, et al. Multicenter analysis of 80 solid organ transplantation recipients with post-transplantation lymphoproliferative disease: outcomes and prognostic factors in the modern era. J Clin Oncol. 2010;28:1038–46.
[43]. Chakrabarti S, Milligan DW, Pillay D, Mackinnon S, Holder K, Kaur N, et al. Reconstitution of the Epstein-Barr virus-specific cytotoxic T-lymphocyte response following T-cell-depleted myeloablative and nonmyeloablative allogeneic stem cell transplantation. Blood. 2003;102:839- 42.

[44]. Saito T, Kanda Y, Nakai K, Kim SW, Arima F, Kami M, et al. Immune reconstitution following reduced-intensity transplantation with cladribine, busulfan, and antithymocyte globulin: serial comparison with conventional myeloablative transplantation. Bone Marrow Transplant. 2003;32:601–8.
[45]. Reshef R, Luskin MR, Kamoun M, Vardhanabhuti S, Tomaszewski JE, Stadtmauer EA, et al. Association of HLA polymorphisms with post-transplant lymphoproliferative disorder in solid-organ transplant recipients. Am J Transplant. 2011;11:817–25.
[46]. Pourfarziani V, Einollahi B, Taheri S, Nemati E, Nafar M, Kalantar E. Associations of Human Leukocyte Antigen (HLA) haplotypes with risk of developing lymphoproliferative disorders after renal transplantation. Ann Transplant. 2007;12:16–22.
[47]. Subklewe M, Marquis R, Choquet S, Leblond V, Garnier JL, Hetzer R, et al. Association of human leukocyte antigen haplotypes with posttransplant lymphoproliferative disease after solid organ transplantation. Transplantation. 2006;82:1093–100.
[48]. Wheless SA, Gulley ML, Raab-Traub N, McNeillie P, Neuringer IP, Ford HJ, et al. Post-transplantation lymphoproliferative disease: Epstein-Barr virus DNA levels, HLA-A3, and survival. Am J Respir Crit Care Med. 2008;178:1060–5.
[49]. Lustberg ME, Pelletier RP, Porcu P, Martin SI, Quinion CD, Geyer SM, et al. Human leukocyte antigen type and posttransplant lymphoproliferative disorder. Transplantation. 2015;99:1220–5.
[50]. Walker RC, Marshall WF, Strickler JG, Wiesner RH, Velosa JA, Habermann TM, et al. Pretransplantation assessment of the risk of lymphoproliferative disorder. Clin Infect Dis. 1995;20:1346–53.
[51]. Sundin M, Le Blanc K, Ringden O, Barkholt L, Omazic B, Lergin C, et al. The role of HLA mismatch, splenectomy and recipient Epstein-Barr virus seronegativity as risk factors in posttransplant lymphoproliferative disorder following allogeneic hematopoietic stem cell transplantation. Haematologica. 2006;91:1059–67.
[52]. Kanakry JA, Kasamon YL, Bolanos-Meade J, Borrello IM, Brodsky RA, Fuchs EJ, et al. Absence of post-transplantation lymphoproliferative disorder after allogeneic blood or marrow transplantation using post-transplantation cyclophosphamide as graft-versus-host disease prophylaxis. Biol Blood Marrow Transplant. 2013;19:1514–7.
[53]. Laberko A, Bogoyavlenskaya A, Shelikhova L, Shekhovtsova Z, Balashov D, Voronin K, et al. Risk factors for and the clinical impact of cytomegalovirus and Epstein-Barr virus infections in pediatric recipients of TCR-alpha/beta- and CD19-depleted grafts. Biol Blood Marrow Transplant. 2017;23:483–90.
[54]. Zhang Q, Zou BH, Lou X, Liu H, Zhang B, Chen H. [An analysis of risk factors and prognosis of Epstein-Barr virus infection after allogeneic hematopoietic stem cell transplantation. Zhonghua Nei Ke Za Zhi. 2016;55:619–23.
[55]. Elstrom RL, Andreadis C, Aqui NA, Ahya VN, Bloom RD, Brozena SC, et al. Treatment of PTLD with rituximab or chemotherapy. Am J Transplant. 2006;6:569–76.
[56]. Ghobrial IM, Habermann TM, Maurer MJ, Geyer SM, Ristow KM, Larson TS, et al. Prognostic analysis for survival in adult solid organ transplant recipients with post-transplantation lymphoproliferative disorders. J Clin Oncol. 2005;23:7574–82.
[57]. Ghobrial IM, Habermann TM, Ristow KM, Ansell SM, Macon W, Geyer SM, et al. Prognostic factors in patients with posttransplant lymphoproliferative disorders (PTLD) in the rituximab era. Leuk Lymphoma. 2005;46:191–6.
[58]. Swinnen LJ, Mullen GM, Carr TJ, Costanzo MR, Fisher RI. Aggressive treatment for postcardiac transplant lymphoproliferation. Blood. 1995;86:3333–40.
[59]. Knight JS, Tsodikov A, Cibrik DM, Ross CW, Kaminski MS, Blayney DW. Lymphoma after solid organ transplantation: risk, response to therapy, and survival at a transplantation center. J Clin Oncol. 2009;27:3354–62.
[60]. Jagadeesh D, Woda BA, Draper J, Evens AM. Post transplant lymphoproliferative disorders: risk, classification, and therapeutic recommendations. Curr Treat Options Oncol. 2012;13:122–36.
[61]. Oton AB, Wang H, Leleu X, Melhem MF, George D, Lacasce A, et al. Clinical and pathological prognostic markers for survival in adult patients with post-transplant lymphoproliferative disorders in solid transplant. Leuk Lymphoma. 2008;49:1738–44.

[62]. Caillard S, Dharnidharka V, Agodoa L, Bohen E, Abbott K. Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation. 2005;80:1233–43.
[63]. Maecker B, Jack T, Zimmermann M, Abdul-Khaliq H, Burdelski M, Fuchs A, et al. CNS or bone marrow involvement as risk factors for poor survival in post-transplantation lymphoproliferative disorders in children after solid organ transplantation. J Clin Oncol. 2007;25:4902–8.
[64]. Styczynski J, Einsele H, Gil L, Ljungman P. Outcome of treatment of Epstein-Barr virus-related post-transplant lymphoproliferative disorder in hematopoietic stem cell recipients: a comprehensive review of reported cases. Transpl Infect Dis. 2009;11:383–92.
[65]. Xu LP, Zhang CL, Mo XD, Zhang XH, Chen H, Han W, et al. Epstein-Barr virus-related post-transplantation lymphoproliferative disorder after unmanipulated human leukocyte antigen haploidentical hematopoietic stem cell transplantation: Incidence, risk factors, treatment, and clinical outcomes. Biol Blood Marrow Transplant. 2015;21:2185–91.
[66]. Gonzalez-Barca E, Domingo-Domenech E, Capote FJ, Gomez- Codina J, Salar A, Bailen A, et al. Prospective phase II trial of extended treatment with rituximab in patients with B-cell posttransplant lymphoproliferative disease. Haematologica. 2007;92:1489–94.
[67]. Trappe RU, Dierickx D, Zimmermann H, Morschhauser F, Mollee P, Zaucha JM, et al. Response to rituximab induction is a predictive marker in B-cell post-transplant lymphoproliferative disorder and allows successful stratification into rituximab or RCHOP consolidation in an international, prospective, multicenter phase II trial. J Clin Oncol. 2017;35:536–43.
[68]. Oertel SH, Verschuuren E, Reinke P, Zeidler K, Papp-Vary M, Babel N, et al. Effect of anti-CD 20 antibody rituximab in patients with post-transplant lymphoproliferative disorder (PTLD). Am J Transplant. 2005;5:2901–6.
[69]. Blaes AH, Peterson BA, Bartlett N, Dunn DL, Morrison VA. Rituximab therapy is effective for posttransplant lymphoproliferative disorders after solid organ transplantation: results of a phase II trial. Cancer. 2005;104:1661–7.
[70]. Choquet S, Leblond V, Herbrecht R, Socie G, Stoppa AM, Vandenberghe P, et al. Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. Blood. 2006;107:3053–7.
[71]. Choquet S, Oertel S, LeBlond V, Riess H, Varoqueaux N, Dorken B, et al. Rituximab in the management of posttransplantation lymphoproliferative disorder after solid organ transplantation: proceed with caution. Ann Hematol. 2007;86:599–607.
[72]. Trappe R, Oertel S, Leblond V, Mollee P, Sender M, Reinke P, et al. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial. Lancet Oncol. 2012;13:196–206.
[73]. Gershburg E, Marschall M, Hong K, Pagano JS. Expression and localization of the Epstein-Barr virus-encoded protein kinase. J Virol. 2004;78:12140–6.
[74]. AlDabbagh MA, Gitman MR, Kumar D, Humar A, Rotstein C, Husain S. The role of antiviral prophylaxis for the prevention of Epstein-Barr virus-associated posttransplant lymphoproliferative disease in solid organ transplant recipients: A systematic review.Am J Transplant. 2017;17:770–81.