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Review Article

Role of Immunotherapy in Post Transplantation Lymphoproliferative Disorders

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Abstract

Post transplantation Lymphoproliferative Disorder is the most severe complication of both solid organ transplantation and hematopoietic stem cell transplantation. It arises in 1-15% of transplanted patients and involves malignant and uncontrolled B cell proliferation. It is due to immunodeficiency resulting from the therapeutic immuno supression in the recipients. The common risk factors of PTLD are age, viral infection including EBV, HCV, CMV, human leukocyte antigen (HLA) alleles and the type of the transplanted organ. The aim of this review is to discuss the patho physiology of the PTLD and various Immuno therapies for PTLD including FDA approved drug such as Brentuximab Vedotin and other drugs that are still in clinical trial.

Keywords: *PTLD; EBV; HSCT; Brentuximab*

Abbreviations : PTLD: Post Transplant Lymphoproliferative Disorder; P-PTLD: Polymorphic Post Transplant Lymphoproliferative Disorder; M-PTLD: Monomorphic Post Transplant Lymphoproliferative Disorder; EBV : Ebstien Bar Virus; SHM: Somatic Hyper Mutation; HHV: Human Herpes Virus; HCV: Hepatitis C Virus; CMV: Cytomegalo Virus; SV 40: Simian Virus 40; SOT: Solid Organ Transplant; ASCT: Autologous Stem Cell Transplant; HSCT: Heterologous Stem Cell Transplant; NHL: Non Hodgkin Lymphoma; LANA: Latency Associated Nuclear Antigen; PSI: Proliferative Signals Inhibitors; IL: Interleukin; FDA: Food and Drug Administration; HTLV: Human T-Lymphocyte Virus; BCL: B cell Lumphoma gene; PAX5: Paired Box 5 gene; TGF : Transforming Growth Factor; IFN: Interferon; miRNA: micro Ribonucleic Acid; GVHD : Graft Versus Host Disease; mTOR : Mammalian Target of Rapamycin

Intruduction/Epidemology

The Post Transplantation Lymphoproliferative Disorders (PTLDs) involves malignant and uncontrolled B-cell proliferation caused by acquired immunodeficiency, resulting from therapeutic immuno suppression in recipients of solid organs or stem cell transplants [1, 2]. The T-cell PTLDS are not common and include EBV, HTLV-1, and HTLV-2 negative, human herpesvirus-8 (HHV-8) [3].

The American Society for Transplantation has recommended that the term PTLD should also be applied to post-transplantation infectious mononucleosis and plasma cell hyperplasia, in addition to neo plastic disease [4]. The prevalence rate varies from 1-15% in the patients with PTLD. The prevalence depends on the immunosuppressive regimen used, the transplanted organ, the age and the EBV immune status of the recipient at the time of transplantation [5]. PTLD may occur within the first year after transplant or late, at one year or longer following transplantation; the former is much more common with an incidence of 224 per 100,000 that falls to 54 per 100,000 by the second year and 31 per 100,000 by the sixth year after organ transplantation.

It includes different type of histopathological and genetic characteristics. The rate of incidence of PTLDs range from 4-10% in lung transplants, 1-6% in cardiac transplants, 1-3% in kidney and liver transplants and 2-6% in combined heart-lung transplants and in up to 20% of small intestine transplants in the adults [6,13].

Etiology/Predisposing Factors

The PTLDS occurs due to the transplantation of organs in the body. WHO classified PTLDs in different categories [14].

Category	Subtype
Early lesions	Reactive plasmacytic hyperplasia
Polymorphic PTLD	Polyclonal
	Monoclonal
Monomorphic PTLD	B-cell lymphomas
	Diffuse large B-cell lymphoma
	Burkitt's/Burkitt's-like lymphoma
	Plasma cell myeloma
	T-cell lymphomas
	Peripheral T-cell lymphoma
	Rare types (gamma/delta, T/natural killer cell)
	Other types
	Hodgkin's disease-like
	Plasmacytoma-like

Table1*: WHO classification of PTLD [14].*

The common risk factors of PTLD are age, viral infections including EBV, Hepatitis C virus (HCV), Cytomegalovirus (CMV) and human leukocyte antigen (HLA) alleles, such as: HLA-A2, -A3, -A8 or -A26. The prevalence rate also varies due to the transplantation of organ [15].

Type of transplanted organ	Location and frequency [%]						
	Kidney	Lung	Liver	CNS	Lymph nodes	GI tract	Disseminated
Kidney	10.3–32	4.4	4.9	11.7	9.5	15.3	14
Liver		4.2	21.8-33	4.2	9.7	12.1	13.3
Heart	0.6	16	8.9	4	4.4	14.3	14.5
Lung and heart–lung	1.4	50–80	4.8	3.4	2.1	4.8	10.3
CNS: Central nervous system; GI: Gastrointestinal.							

Table2: *Location and incidence of PTLD in organ transplantation [15].*

Pathophysiology/Molecular Basis

I. Patho physiology/molecular basis of PTLDs: The DNA mutations such as RhoH/TTF, PAX5, PIM1, C-MYC; chromosomal translocation such as BCL-2, C-MYC, IGH and polymorphisms in both the host (TGF-beta, IFN-gamma, HLA, IL-10) and the EBV genome involves the development of B-cell PTLD Table3.

DNA Mutations

Nucleotide-level variations can be caused by aberrant somatic hyper mutation (SHM) during the germinal center reaction. SHM normally targets the immunoglobulin variable (IgV) genes, in orderto generate high-affinity antibodies [16]. The abnormal SHM is considered to be a tumor-specific pathogenetic process, targeting proto-oncogenes, such as RhoH/TTF, PAX5, PIM1, c-MYC and has been reported in lymphoma to be independent of the immune and EBV status of the host [17,18]. Abnormal SHM may also introduce stop codons in Ig genes, resulting in crippled Bcr. The LMP2A may work as a Bcr substitute in these cells, which provides the necessary survival signals [19].

Chromosomal Translocation

The most common aberrations are trisomies of chromosome 9 and/or 11, which are associated with EBV positivity; followed by translocations involving and these are observed 14q32 (IGH, TCL1), 3q27 (BCL-6) and 8q24.1 (C-MYC) [20]. There were two studies, which reported different frequencies of cytogenetic abnormalities in PTLD (57% of Polymorphic Post-transplant lymphoproliferative disease (P-PTLD), 33% of P-PTLD, 46% of Monomorphic Post-transplant lymphoproliferative disease (M-PTLD) and 75% of M-PTLD). These differences suggest that part of PTLD cases are caused by the epigenetic alterations, mutations and oncogenic EBV signaling [21,23]. The PTLD is characterized by distinct genetic abnormalities, such as loss of 4q, 17q and Xp, including various changes, which are common in lymphoma arising in the immuno competent patients, but with different frequencies (gains of 11p, 12q, 12p, 18q21: BCL-2 and MALT, 21q 3q27: BLC-6 and loss of 1p, 6q, 9p, 17p13: TP53) [24].

EBV Genome

In the EBV genome, mRNAs expressed during latency are encoded in BART clusters (in the introns of BART gene) and BHRF-1 clusters (in the 3′ UTR of the BHRF-1 open reading frame) and can regulate cellular genes, possibly conferring resistance to apoptosis [25]. The BHRF-1 encoded protein is the viral homolog of BCL-2. In addition, the EBV mRNAs can down regulate viral proteins, such as 2A and LMP1, which indicates a possible mechanism for immune escape [25]. Various studies have suggested that EBV encoded mRNA are probably interrupting with immune response against different EBV infected cells [26]. Sometimes the viral mRNA expression is very complex and has been shown to be tissue-specific and dependent on the pattern of EBV gene expression [27]. Apart from its own mRNAs, EBV can simultaneously induce cellular mRNAs for the modulation of lymphocyte homeostasis (miR-155) and interferon responses (miR-146a) [28,29].

EBV comprises different viral proteins, which interact with or show homology to a range of anti-apoptotic human molecules, cytokines and signal transducers. These viral proteins are EBV nuclear antigens-1 (EBVNA1), EBNA2, EBNA3A, EBNA3B, EBNA3C, EBNA-LP and LMP-1, LMP2A and LMP2B. Along the membrane of these proteins, EBV-encoded non-translated RNAs (EBER) are reproduced in latently infected B-cells [30,33].

EBNA1 is a DNA-binding nuclear phosphoprotein and it is necessary for the maintenance and replication of the episomal EBV genome, EBNA2 is a transcriptional co-activator, which controls various cellular genes concerned in the survival and proliferation, it also controls both viral latency genes such as LMP1 and LMP2. The LMP1 is the main transforming protein of EBV (Figure2) and LMP2A is an integral membrane protein, which includes a tyrosine-based activation motif (ITAM) immuno receptor (Figure2) [30,35].

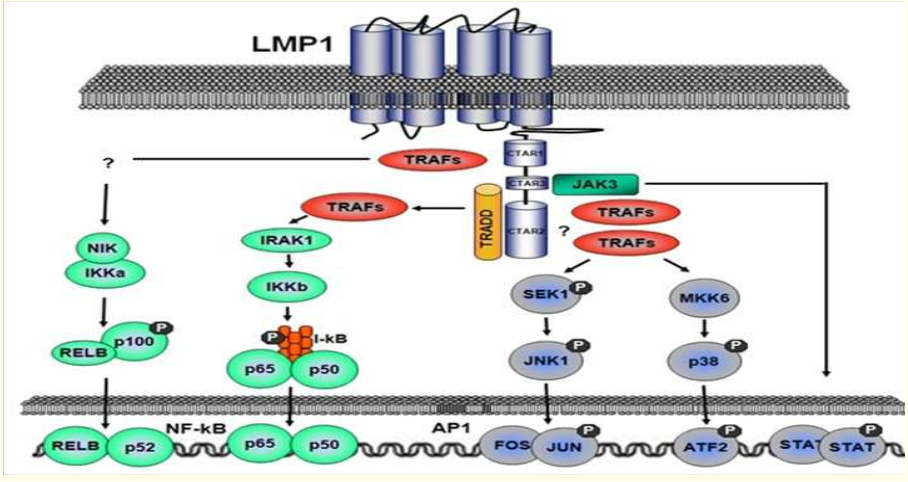

Figure 1*: The role of LMP1 in PTLD [17].*

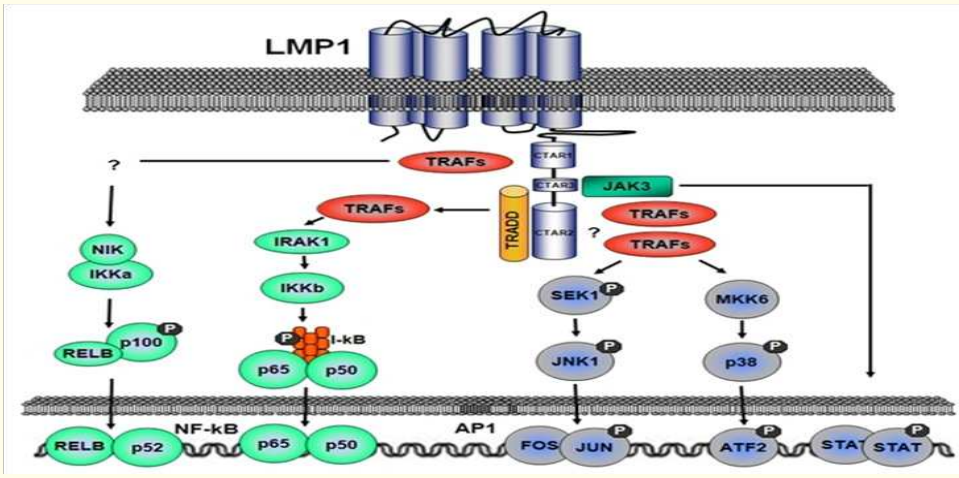

Figure 2: *Signaling relationship between LMP2 and BCL in PTLD [36].*

The EBNA-2 is a transcriptional co-activator, which plays a major role in the EBV-driven B-cell growth transformation process. It activates an array of viral and cellular target genes. Moreover, it initiates a cascade of events, which cause cell cycle entry and proliferation of the infected B-cells.

Human Herpes Virus 8 (HHV-8)

HHV-8 is a double stranded DNA virus, belonging to the γ-herpesvirus family. It establishes a life-long latent infection similar to EBL, in which the viral DNA persists as an episome in the nuclei infected cells [37, 38]. It is also known as KSAH. The HHV-8 encoded latency associated nuclear antigen-1 (LANA1) interacts with the p53 and suppresses its transcriptional activity. It has the ability to induce apoptosis [39]. LANA-1 also binds to the Rb protein, therefore delivering the E2F transcriptional factor that up regulates the various genes involved in the progression of the cell cycle [40]. The LANA-1 is able to induce the IL-6 expression through the interaction with AP1 transcription factor. The v-cyclin gene encodes a homologue of human cyclin D2 [41].

Simian Virus 40

Although there are two primary reports, which express a high prevalence of Simian Virus 40 (SV40) in the NHL including immunodeficiency-related NHL, the association between SV40 and PTLD and more in general NHL has been subsequently denied by large molecular, immunohistochemical and serological Studies [42,46].

Hepatitis C Virus

The present pathologic theory holds that Hepatitis C Virus (HCV) may act on the B-cells, indirectly through chronic antigen stimulation, as suggested by the identification of molecular clues of antigen stimulation in HCV-related NHL and by the HCV specific IGV expression, in a fraction of HCV-related NHL [47].

Genetic alteration		Frequency
BCL6 gene	(1) Rearrangement	Rare in PTLD
	(2) SHM	50% of PTLD
c-Myc gene rearrangement		100% PT-BL
BCL2 gene	(1) Rearrangement	Very rare in PTLD
	(2) Amplification	A proportion of PTLD
P53 gene mutation/deletion		Small proportion of mPTLD

Translocations involving IG genes		A small proportion of PTLD. Rarely in florid follicular hyperplasia in post transplant setting
PAX5 gene	(1) Rearrangement	Very rare in PT-DLBCL
	(2) SHM	Very rare in PT-DLBCL
	(3) Amplification	A proportion of PTLD
Chromosomal gains	(1) 3q27, 7q, 8q24, 12q, 12p, 18q21, 21q	
	(2) 5p and 11p	PT-DLBCL = iDLBCL
	(3) 6q25.3	Recurrent in PT-BL
	(4) 1q, 11q, and of chromosome 7	PT-DLBCL
Chromosomal loss	(1) 1p, 6q, 9p, and 17p13	Common to PTLD and lymphomas immune competent patients
	(2) 4q, 17q, and Xp	In PTLD but not common in other lymphomas
	(3) 12p, 4p, 4q, 12q, 17p, and 18q	Frequent in PT-DLBCL
	(4) 11q25	Recurrent in PT-BL
	(5) 2p16.1 (FRA2E)	30% of PT-DLBCL (both in EBV positive and negative cases)
	(6) 17p	PT-DLBCL
Aberrant hyper methylation of	(1) MGMT	75% pPTLD and 93% mPTLD.
	(2) DAP-kinase	75% mPTLD
	(3) TP73	20% mPTLD
	(4) SHP1	~77% PT-DLBCLs, 75% pPTLDs, 66% PT-BLs
	(5) CDKN2A	A small proportion of mPTLD
PT-BL: Post transplant BL; PT-DLBCL: Post transplant diffuse large B cell lymphoma; iDLBCL: Immuno competent diffuse large B cell lymphoma.		

Table 3*: Various Genetic Alterations among Ptlds [48].*

Immunotherapy for PTLDs

Monoclonal Antibodies

BrentuximabVedotin: Brentuximab vedotin is a FDA approved CD30-directed antibody-drug conjugate indicated for the treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients, who are not the potential candidates for ASCT [49].

The most common adverse effects are rash, vomiting, fatigue, neutropenia, pyrexia, cough, diarrhea, peripheral sensory neuropathy, anemia, thrombocytopenia, nausea and upper respiratory tract infection.

The treatment with Brentuximab vedotin produces peripheral neuropathy. Stevens-Johnson syndrome and Tumor lysis syndrome has been reported. Brentuximab vedotin can cause fetal harm in pregnant women. Hence, it should not be given to the pregnant women.

Rituximab: It is a recombinant chimeric murine/human antibody directed against the CD20 antigen, a hydrophobic transmembrane protein located on normal pre-B and mature B-lymphocytes. Following binding, rituximab triggers a host cytotoxic immune response against CD20-positive cells. Rituximab is an only agent, which has 63% efficacy for the treatment of EBV-PTLD and it is also used as a first-line treatment in different transplant centers [50].

The Rituximab targets CD20 (+) tumors and also reduces the B-cells in EBV-PTLD. Rituximab may change the ratio of EBV-infected B-lymphocytes to EBV-specific cytotoxic T-cells in favor of anti-tumor or anti-viral immune response. A study stated that Rituximab-

sensitive EBV-positive lymphoma cells showed resistance to the treatment with Rituximab after the transfection with LMP-1. This LMP 1 transfection leads to Akt inhibition and Akt phosphorylation restores Rituximab sensitivity of these cells [51].

Simultaneous use of Rituximab with live vaccines might increase the risk of infection through the live vaccine. Main Side Effects are Infusion reactions, neutropenia, and hypogammaglobulinemia. Rituximab is a protective, successful and effective monoclonal antibody for the treatment of PTLD especially when; it is used in combination with chemotherapy [52,57].

No. Of patients	Partial remission	Complete remission (%)	Overall survival (%/years)	Mean time of follow-up (months)
17	5.9	52.9	56/3	24.2
43	16.2	44.2	67/1	12
11	9.1	54.5	54,5/1	10
17	20	60	64/1	60
26	7.6	57.6	73/1	8
59	40	73/3		

Table 4: *Efficacy of Rituximab in PTLD patients after Solid Organ Transplant (SOT).*

Basiliximab: A recombinant, chimeric, human-murine monoclonal antibody directed against the alpha subunit of the interleukin-2 receptor (IL-2R alpha) with immunosuppressant activity. Basiliximab selectively binds to and blocks IL-2R alpha, expressed on the surface of activated T-lymphocytes, thereby preventing interleukin-2 binding and inhibiting the interleukin-2-mediated activation of lymphocytes.

Drug	Clinical trial identifier number	Phase	Study design	Target
Basiliximab	NCT02342782	Phase I	Safety Study, Open Label	IL-2R alpha

Table 5*: Non-FDA Approved MABs [58].*

Mammalian Target of Rapamycin Immunotherapy (mTOR): There is no mTOR inhibitor that is currently approved by FDA for PTLDs. However, many mTOR inhibitors are under clinical trials in phase I, II and III as in 9 Table 6 below:

Drug	Clinical trial identifier number	Phase	Study design	Target
Sirolimus	NCT01251575	Phase II	Open label, Efficacy Study	mTOR
Everolimus	NCT00918333	Phase I, II	Open label, Safety/Efficacy Study	mTOR

Table 6*: Non-FDA Approved mTOR drugs [59, 60].*

Kinase Inhibitors Immunotherapy: There is no kinase inhibitor that is currently approved by FDA for PTLDs. However, the drug that is under clinical trials in phase I, II and III is listed in Table 7 below:

Sunitinib: It is an indolinone-based tyrosine kinase inhibitor having anti-neo plastic activity. It blocks VEGFR2, PDGFRb, c-kit, thereby inhibiting angiogenesis and cell proliferation. This agent also inhibits Fms-related tyrosine kinase 3 (FLT3).

Drug	Clinical trial identifier number	Phase	Study design	Target
Sunitinib malate	NCT00890747	Phase I	Open label, Safety Study	VEGFR2, PDGFRb, FLT3, c-kit

Table 7: *Non-FDA Approved kinase inhibitor drugs [61].*

Bortezomib: It is a proteasome inhibitor drug with anti-neo plastic activity. It reversibly inhibits the 26S proteasome, a large protease complex that degrades ubiquinated proteins. It also inhibits NF-kappa B, thereby interfering with NF-kappa B-mediated cell survival, tumor growth and angiogenesis.

Drug	Clinical trial identifier number	Phase	Study design	Target
Bortezomib	NCT01058239	Phase II	Non-Randomized, Open label, Efficacy Study	KIT, CSF1R, FLT3

Table 8: *Non-FDA Approved proteasome inhibitor drugs [62].*

Vaccine Immunotherapy: There is no vaccine that is currently approved by FDA for PTLDs. However vaccines that are under clinical trials in phase I, II, and III are listed in Table 9 below:

Drug	Clinical trial identifier number	Phase	Study design	Target
Autologous EBV transformed BL cell vaccine	NCT00278200	Phase I	Non-Randomized	Cancer cells
EBV-specific autologous CTL	NCT00063648	Phase I	Non-Randomized, Open label, Safety/ Efficacy Study	Cancer cells

Table 9: *Non-FDA Approved vaccines [63, 64].*

Cytokine therapy

Interleukin-15: A fusion protein complex composed of a mutated form of the cytokine interleukin (IL)-15 (IL-15N72D) and a soluble, dimeric IL-15 receptor alpha (IL-15Ra) Fc fusion protein (IL-15Ra-Fc) (IL-15N72D/IL-15Ra-Fc) with potential antineoplastic activity. Upon administration, super agonist interleukin-15: interleukin-15 receptor alpha Su/Fc fusion complex ALT-803 binds to the IL-2/IL-15 receptor beta-common gamma chain (IL-2Rbetagamma) receptor on NK and CD8+ T lymphocytes, which activates and increases the levels of NK cells and memory CD8+(CD44high) T-cells. The memory T-cells enhances the secretion of the cytokine interferon-gamma (IFN-g), which further potentiates the immune response against tumor cells. This may increase tumor cell killing and decrease tumor cell proliferation. IL-15 regulates CD8+ T and NK cell development, activation and proliferation. By coupling IL-15 to IL15Ra-Fc, this agent has a prolonged drug half-life and shows an increased ability to bind IL-2Rbetagamma, which enhances its immune stimulatory activity as compared to IL-15 alone.

Drug	Clinical trial identifier number	Phase	Study design	Target
Interleukin-15	NCT01572493	Phase I	Safety Study, Open Label	Cancer cells

Table 10: *Non-FDA Approved miscellaneous drugs [65].*

Reduction or Modification of Immuno suppression: The reduction of pharmacologic immuno suppression (RI) can be a useful option for the treatment of EBV-PTLD in some cases, although this strategy must be balanced against the risk of transplant rejection. As an alternative to RI, modification of the immuno suppression regimen to include agents that have potential anti-tumor and anti-viral properties is an attractive option, allowing treatment of the EBV-PTLD, while maintaining the level of immuno suppression necessary to prevent graft rejection and GVHD. The mTOR inhibitors have been explored in PTLD given their anti-tumor properties in other settings [66,67].

Adoptive Cellular Immunotherapy: Adoptive T-cell therapy with EBV-cytotoxic T-cells (EBV-CTLs) has been used for the prevention or treatment of EBV-PTLD and it has been proven to be safe and effective, even in patients with relapsed or refractory disease [68,69]. In healthy people, virus-induced proliferation is kept under control by cell-mediated immunity elicited at the moment of primary infection.

As immuno compromised transplant recipients lack appropriate EBV-specific cell-mediated immunity, restoration can be obtained by administration of selected, ex-vivo expanded, virus-specific T-cells [70,71].

The requirement of generation of autologous lymphocytes results from the fact that more than 90% of PTLDs arising after the SOT derive from the recipient B-cells. Generally, PTLDs appears from the donor B-cells in the hematopoietic stem cells recipients or the bone marrow [72]. Unfortunately, in rapidly progressive forms of PTLD, the two to three months time span required for the production of autologous CTL implies that allogeneic CTL in this setting is unrealistic. Both allogeneic and autologous CTL administration has been shown to be effective, well tolerated and safe approaches for PTLD prophylaxis and treatment [73,75].

Proliferation Signal Inhibitors (PSIs)

In spite of the fact that Everolimus and Sirolimus were found to have anti-proliferative potential in the PTLD-derived cell lines *in-vitro* as well as in solid tumors in a mouse *in-vivo* model of PTLD, one must be careful when transposing these conclusions into the treatment of human PTLD [76,77]. Despite the potential of PSI in the management of PTLD, the UNOS study unexpectedly reported a two-fold increase in PTLD in RTRs, treated with Sirolimus after transplantation [78,79]. It is therefore very difficult to draw definitive conclusions in relation to the use of PSI in the PTLD treatment.

Antiviral Agents

Taking into consideration the patho physiology of PTLD, it is unlikely that anti-viral agents, such as Ganciclovir or Acyclovir, even given in high doses, will be effective and useful in the treatment of PTLD and especially, when it is used as single agent. Since, the EBV genome is incorporated into the infected B-cell; these cells express a limited number of viral proteins that could be eliminated by these agents. The prophylaxis, rather than treatment is currently indicated for high-risk patients (EBV+ donor and EBV- recipient pair), but the limited number and non-randomized character of related trials preclude the definitive conclusions [80]. All these agents can be helpful in the treatment of PTLD and especially in the EBV-Seronegative patients and/or over immuno suppressed recipients as well as in the EBV-replicative forms of PTLD such as lymphoid hyperplasia [81].

Therapy	Clinical Applications
Adoptive T-cell therapy	
Donor lymphocyte infusions	PTLD after HSCT
Donor-derived (allogeneic) EBV CTLs (LCL- or EBV-peptide–stimulated)	PTLD after HSCT
Autologous EBV CTLs (LCL- or EBV-peptide–stimulated)	PTLD after SOT, HL, NPC; other EBV+ malignancies
Third-party HLA-matched EBV CTLs	PTLD after SOT or HSCT; other EBV+ malignancies
Inhibitors of EBV-activated signaling pathways	
Dasatinib (LMP2 activation of Lyn/Syk)	
Akt inhibitor MK-2206 (LMP1, LMP2 activation of PI3K/Akt/mTOR)	Lymphoma, NPC
Rapamycin (LMP1, LMP2 activation of PI3K/Akt/mTOR)	
Bortezomib (LMP1 activation of NF-κB)	Lymphoma, PTLD, NPC
Brentuximabvedotin (CD30 signaling)	EBV/CD30+ lymphoma
Lytic inducers (coupled with anti-herpes virus agents[b])	
Phenylbutyrate, arginine butyrate (HDAC inhibitors)	Lymphoma, NPC
Other HDAC inhibitors	NPC
Parthenolide	
Arsenic trioxide	
5-Azacytidine	

Zidovudine (± chemotherapeutics)	PCNSL
Gemcitabine + valproic acid	NPC
Bortezomib (± gemcitabine)	Lymphoma, PTLD, NPC
EBV vaccines	
Recombinant EBV gp350	Prevention of primary infection
Recombinant modified vaccinia virus Ankara EBNA1/LMP2	NPC

Table 11: *Different therapies for EBV associated malignancies [82].*

HSCT: Hematopoietic Stem Cell Transplant; LCL: Lymphoblastoid Cell Line; NPC: Nasopharyngeal Carcinoma; HDAC: Histone Deacetylase; PCNSL: Primary Central Nervous System Lymphoma.

[a]Includes case reports and series, in addition to completed and ongoing clinical trials.

[b]Ganciclovir, valganciclovir.

Conclusion

The PTLDs are related to organ transplantation. It is mainly caused by EBV and sometimes may be due to the HIV and HTLV-1. It mainly occurs in patients with weakened immune system.

Rituximab is the only FDA approved immuno therapeutics for the treatment of Hodgkin lymphoma. There are some adoptive T-cell therapies, monoclonal antibodies, proteasome inhibitors and anti-viral agents, which are effective in the treatment of PTLDs. There are various targeted therapies with several immuno therapeutics, but they are under clinical trials. The researchers are still challenged to explore the innate and adaptive immune systems. The recent activities have increased our understanding of the tumor microenvironment, various immunotherapeutic modalities, or combination therapies (like chemotherapy with immunotherapy) in various clinical trials. The complete perspective of immunotherapy treatment has not been realized or utilized. Proper preclinical and clinical designs are the important pillars in understanding the future of immunotherapy in treating cancer patients.

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