Chapter

Immunosuppression and Viral Infections

Seema Naik, Kevin Rakszawski, Joseph Cioccio, Hong Zheng and Hiroko Shike

Abstract

Immunosuppression is commonly used for prevention of graft rejection in solid organ transplantation (SOT) and prevention of graft versus host disease in hematopoietic allogeneic stem cell transplant (ASCT). In ASCT, immunosuppression is used to control GVHD and can be tapered off within 6–12 months after transplantation. SOT recipients require lifelong immunosuppression to prevent graft rejection, making them susceptible to serious viral infections including EBV PTLD. EBV PTLD occurs within the first 6 months following ASCT prior to effective reconstitution of cytotoxic T lymphocytes (CTL). Our understanding on EBV-related PTLD is mostly extrapolated from SOT-associated PTLD. Features of conditioning and use of serotherapy remain important in development of EBV PTLD. Other viral infections that occur early post-transplant include CMV, HHV6, BK, and adenovirus, and usually correspond to degree of immunosuppression post-transplant. These infections are associated with significant morbidity and mortality. However, the current literature lacks information on outcomes of viral infections related to immunosuppression. Alternative donor ASCT are now more common, and patients are more susceptible to multiple viral infectious complications at the peak of immunosuppression and require monitoring for viral infections in these immunosuppressed patients.

Keywords: immunosuppression, EBV PTLD, CMV, HSV, VZV, BK, HHV6

1. Immunosuppression

Immunosuppression is commonly used for prevention of graft rejection in solid organ transplantation (SOT) and prevention of graft versus host disease in hematopoietic allogeneic stem cell transplant (ASCT). In solid organ transplantation (SOT), the donor grafts are recognized as non-self by the recipient's immune system. The recipient immune system can cause T-cell-mediated rejection and antibody-mediated rejection at any time. Immunosuppression is critical to control the recipient immune system and protect donor organs from rejection. Therefore, immunosuppression is generally necessary as long as the patient retains a viable donor graft.

In allogenic hematopoietic cell transplantation, donor-derived hematopoietic stem cells and lymphocytes replace the hematopoietic system as well as the immune system of the recipient. While donor T-cells provide anti-pathogen and anti-tumor activity to the recipient, donor-derived alloreactive T-cells are responsible for graft versus host disease (GVHD). Immunosuppression is used to control acute and chronic GVHD. However, alloreactive T-cells are eventually eliminated in most patients, and immunosuppression can be tapered off within 6–12 months after transplantation in ASCT. Solid organ transplant recipients, on the other hand, require lifelong immunosuppression to prevent graft rejection, making them susceptible to EBV virus mediated post-transplant lymphoproliferative disorder (PTLD). In ASCT, some patients who develop chronic GVHD also need prolonged immunosuppression requiring monitoring and treatment of complications related to serious viral infections.

In cord transplant recipients and, more recently, in haploidentical transplant and mismatched transplant patients, with the effect of antithymocyte globulin (ATG) and other T-cell depleting regimens, patients are even more susceptible than usual to either single or multiple viral infectious complications at the peak of immunosuppression. Use of TNF receptor blockers including etanercept and infliximab for GVHD or Crohn disease, the use of other interleukin inhibitors for skin GVHD, and other autoimmune disorders are additional examples of ongoing immunosuppression that would require monitoring for viral infections and complications in these immunosuppressed patients.

The most common immunosuppression to prevent GVHD is the use of calcineurin inhibitors tacrolimus and cyclosporine. Calcineurin is an essential enzyme in the activation of T-cells. Both tacrolimus and cyclosporine have similar mechanisms of action and efficacy. In the post-transplant period, monitoring of tacrolimus and cyclosporine serum levels is performed as a surrogate for depth and degree of immunosuppression. In the early post-transplant period, a higher serum levels are essential until alloreactive T-cells are eliminated, at which point lower serum levels can still prevent GVHD. Other immunosuppressants used post-transplant include mycophenolate mofetil and mycophenolate sodium, which exhibit a cytostatic effect on T- and B-lymphocytes. Cyclophosphamide is now routinely given in the post haploidentical or mismatched transplant setting to reduce the incidence of GVHD by selective removal of alloreactive donor T-cells.

In the post-treatment phase beyond 100 days, the presence of chronic GVHD is the main determinant of infection. Patients who developed acute GVHD experience approximately 60% more infections than patients who do not develop acute GVHD. Furthermore, patients who experience chronic GVHD have their immunosuppression increased or restarted, therefore increasing the risk of infection.

2. EBV infection

EBV PTLD develops in approximately 1% of patients post ASCT. It is highly related to EBV reactivation. Risk factors that associate with high incidence of EBV-related PTLD include older age at transplant, T-cell depletion-containing conditioning regimens, antithymocyte globulin (ATG) use, and grafts derived from unrelated or HLA-mismatched donors [1–5]. PTLD in ASCT patients occurs in the younger age group, with shorter duration of onset as compared to (SOT) solid organ transplantation.

EBV PTLD occurs more commonly in pediatric patients than in adults because more pediatric patients are EBV naïve. PTLD can occur during the post-transplant period after both myeloablative and non-myeloablative ASCT. The degree and duration of immunosuppression plays a major role in the development of PTLD. Cytotoxic T lymphocytes (CTLs) provide a defense mechanism against EBV-infected B cells in immunocompetent individuals. However, T cell function is impaired post allogeneic transplant which leads to the development of PTLD. In vivo T cell depletion (TCD) with antithymocyte globulin (ATG) or alemtuzumab (AL) is commonly used in ASCT. As reduced intensity conditioning (RIC) and matched unrelated donor (MUD) transplants are now being performed more frequently, ATG and AL have become integral components of preparative regimens to facilitate engraftment and reduce the incidence and severity of GVHD. Delayed T cell reconstitution following T cell depletion accounts for infectious complications including PTLD, which is associated with increased mortality [3, 4].

EBV PTLD can occur later in the most severely immunocompromised patients with additional risk factors such as donor and recipient mismatch, graft manipulation with T cell depletion as well as the degree and duration of immunosuppression. Prevention of PTLD involves limiting the duration and degree of immunosuppression, while still maintaining the adequacy of the donor graft. Achieving a balance of reduction in immunosuppression and preventing graft rejection or graft versus host disease can be challenging. Antiviral prophylaxis may also play a role in preventing PTLD. The use of antiviral agents such as acyclovir, valganciclovir, and ganciclovir are common for HSV, CMV, and EBV prophylaxis, though data is very limited for prevention of EBV PTLD [2–5].

EBV monitoring of high-risk patient facilitates preemptive rituximab or tapering of immunosuppression upon viremia proceeding PTLD. Successful clearance of EBV and prevention of PTLD has been reported with B-cell depletion by rituximab [6–8]. On the other hand, antiviral agents, such as acyclovir, ganciclovir, and valganciclovir are not widely used for prevention, due to limited data. [2–5]. The use of "Off-the-shelf," third-party EBV-specific CTLs is a new promising approach to treat refractory PTLD to rituximab or immunosuppression tapering [3]. Treatment algorithm for EBV PTLD is as shown in **Tables 1** and **2**.

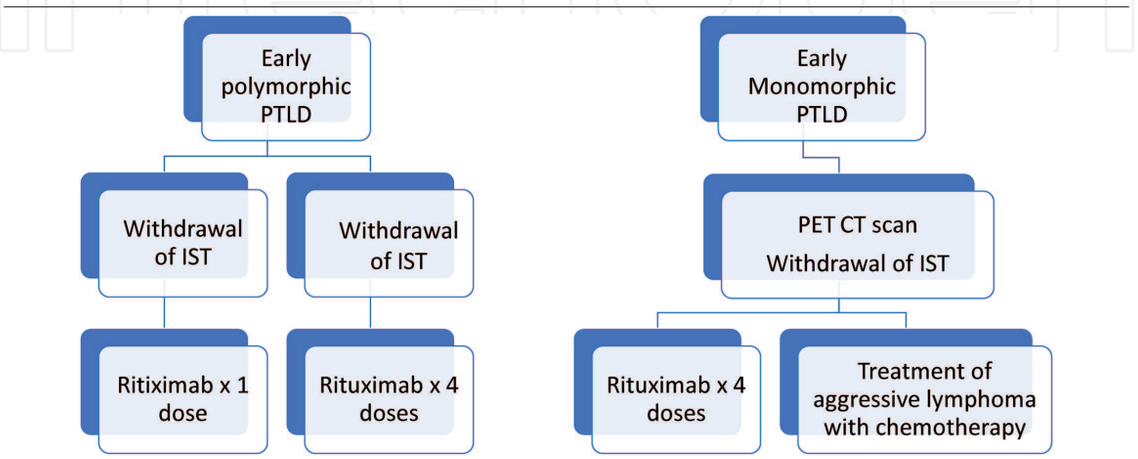

Table 1.
Treatment algorithm for EBV positive PTLD.

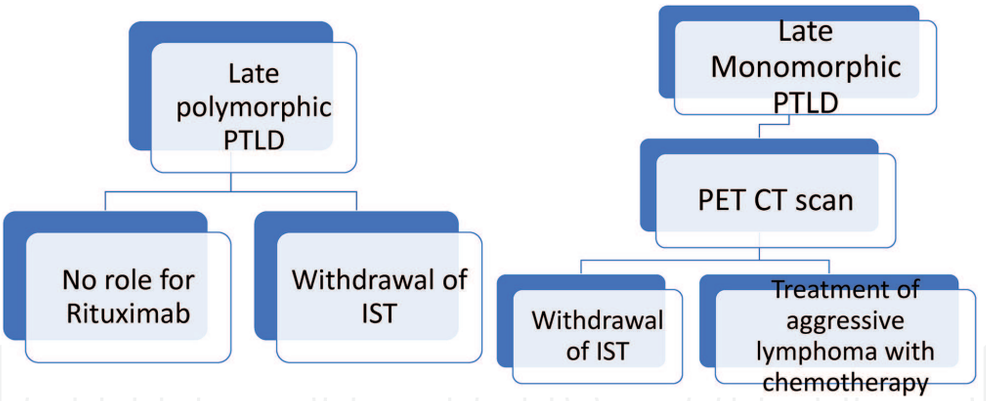

Table 2.
Treatment algorithm for EBV negative PTLD.

3. Other viral infections

Other viral infections that occur early post-transplant include CMV, HHV6, BK, and adenovirus, and usually correspond to degree of immunosuppression post-transplant [4, 9]. However, the current literature lacks information on outcomes of viral infections as well as the influence of graft sources, such as comparison of outcomes between umbilical cord blood transplant (UCBT) and haploidentical transplant (haplo) with post-transplant cyclophosphamide (PTCy) [10]. These infections usually occur within in early post-transplant period prior to effective immune reconstitution [1, 11, 12]. Despite advances in antiviral therapy, severe infections still remain a major cause of death after alternative donor ASCT [5, 9, 13].

In a prospective analysis of immune reconstitution in double UCBT recipients and matched unrelated donor (MUD) recipients, CD3 recovery was significantly delayed in the double UCBT group compared with MUD group for as long as 6 months after ASCT [5, 9, 13]. These unique properties of UCBT may contribute to a high risk of infection reported in some studies. Novel strategies are now being developed to combat viral infections including the virus-specific or trivirus-specific (adenovirus, Epstein-Barr virus, and cytomegalovirus) CTLs [14–16]. Early diagnostic information regarding viral infections is critically important in the current era of emerging new therapies for viral infections.

4. CMV infection

CMV infection occurs in 50–80% of the population and CMV virus is maintained in a latent reservoir in mononuclear leukocytes. Containment of CMV in its latent state affects a large proportion of host immune repertoire. In young adults, 1–2% of CD4 and CD8 T cells are CMV-reactive, which rise to up to 30–40% in the elderly. For the majority of CMV-infected individuals, asymptomatic reactivation is effectively countered by innate and adaptive immunity. In the immunocompromised ASCT patients, unconstrained viral replication and dissemination can lead to CMV disease, and increased mortality due to end-organ damage. The efficacy of conventional antiviral therapies including ganciclovir and foscarnet is limited in the setting CMV disease with end-organ involvement [17].

CMV-seropositive patients will experience CMV dissemination after ASCT, particularly in the context of transplant using T cell-depleted or matched unrelated

donor (MUD) grafts. In CMV-seronegative patients, CMV infection is prevented through selection of CMV-seronegative grafts, but 20–40% of CMV-seronegative patients who receive CMV-seropositive grafts develop primary CMV infection. Untreated, 50% of ASCT patients with CMV reactivation will develop CMV disease. The current clinical practice uses close surveillance monitoring of CMV DNA burden by quantitative PCR (qPCR). Preemptive antiviral pharmacotherapy and prophylactic therapy strategies are used to reduce the incidence of CMV disease after ASCT. Novel antiviral pharmacotherapies including maribavir, letermovir, and brincidofovir are under clinical trial development but have not yet clearly demonstrated superiority or lesser toxicity compared to conventional antiviral agents [17].

5. Adenovirus viral infections

Adenovirus (AdV) infections are much more common in pediatric patients (20–26%) than in adults (9%) undergoing ASCT. In the severely immunocompromised patients, Adv can cause severe respiratory viral disease, hepatitis, and colitis. Other complications include hemorrhagic cystitis and adenoviral keratoconjunctivitis. AdV infection can cause subclinical viremia, viremia with disease symptoms, and disseminated disease. The incidence of disseminated disease is 1–7% with mortality of 8–26%. Rapidly increasing or persistent viremia is associated with the occurrence of severe adenoviral disease both in children and in adults. Monitoring of the viral load by blood AdV qPCR is far superior with high sensitivity. A study in adult ASCT recipients has reported an infection rate of 2.5% with pneumonia occurring in 24% of cases as the most common cause of death. Viral gastrointestinal shedding prior to transplant is found to be associated with increased risk of viremia after ASCT [18]. Treatment of adenoviral infections include Cidofovir, brincidofovir (compassionate use in children) and use of IVIG as well as taper of immunosuppression. More recent studies have used nucleofection to introduce DNA plasmids encoding multiple immunogenic antigens from CMV, EBV, and adenovirus into APCs to control lethal adenoviral infections.

6. HHV6 infection

Human herpesvirus 6 (HHV6), a member of β-herpesvirus subfamily, establishes primary infection as exanthem subitum in the normal pediatric population. With time, it establishes latency in $CD34^+$ cells, monocytes, and macrophages, similar to cytomegalovirus (CMV). Over the last decade, HHV6 has been increasingly recognized as an opportunistic and potentially life-threatening pathogen after ASCT [1–5, 9, 13–16, 18]. Following ASCT, HHV6 infections are caused by reactivation of the virus from latency. HHV6 reactivation is detected in the blood of 40–60% of patients after ASCT, most often by use of qPCR for viral-specific sequences.

HHV6 viremia has been reported in association with varying organ dysfunction and clinical syndromes including delayed/impaired platelet recovery, myelosuppression, encephalitis, fever, rash, hepatitis, pneumonitis, gastroduodenitis, CMV reactivation, and GVHD.

Treatment indications are uncertain in patients with HHV6 viremia following ASCT. HHV6 encephalitis is potentially fatal and is a common indication for treatment. Only one trial evaluated preemptive treatment of HHV6 based on a positive qPCR test. The development of reliable clinical guidelines for the management of

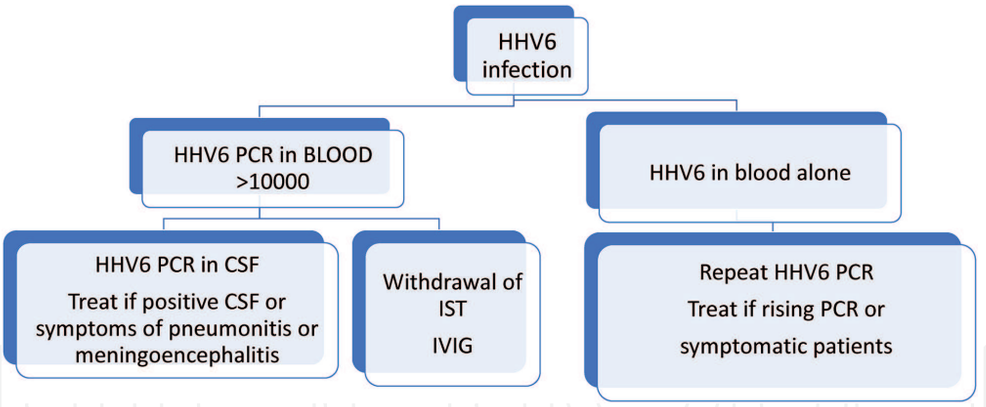

Table 3.
Treatment of HHV6 infection.

HHV6 viremia in ASCT recipients has historically been limited by the lack of specificity of viremia testing and by the lack of specific HHV6 clinical syndromes. It is also confounded by the occurrence of asymptomatic viremia, which often resolves without intervention. Treatment algorithm for HHV6 is as shown in **Table 3**.

7. BK virus infection

The BK virus infection is associated with hemorrhagic cystitis in ASCT recipients. Treatment interventions are mainly focused on supportive measures including hyperhydration, continuous bladder irrigation, and topical agents to alter the bladder mucosal lining. In the recent years, BK virus PCR in the urine and plasma has helped with early detection of BK virus infection and BK hemorrhagic cystitis (BK-HC) as higher urine and plasma viral loads are associated with disease manifestation including BK-HC [19, 20].

Other treatments of BK-HC aim at repair and regeneration of the urothelial mucosa through hyperbaric oxygen therapy or by topical application of fibrin. Use of hyperbaric oxygen has limited availability and also the risk of barotrauma and claustrophobia [19]. Finally, topical fibrin glue applications to the damaged bladder mucosa to achieve hemostasis through cystoscopy have been reported in single-center retrospective series of 35 patients with complete response rate of 83%. Several compounds to reduce bleeding have been used in small studies which include FXIII concentrate, intravesical sodium hyaluronate, estrogens or choreito extract granules with response rates between 50 and 100% [19]. Brincidofovir, a lipid conjugate of cidofovir has a potent and long-lasting inhibitory effect on BK virus replication in vitro studies but no data are available on the clinical use in BK nephropathy after ASCT. Brincidofovir may have the future indication for symptomatic BK-HC considering the absence of alternative antivirals with a better safety and tolerability profile [19, 20].

The reduction of immunosuppression has been used successfully in kidney transplant patients to prevent and/or treat BK nephropathy, but there is no evidence that it has a favorable risk/benefit ratio in ASCT patients due to the risk of worsening donor alloreactivity and severity of GVHD. Unlike for BK nephropathy, there is no documented benefit in using intravenous immunoglobulin (IVIG) for BK-HC. Extrapolating from use in BK virus nephropathy in renal transplant patients, cidofovir and leflunomide are only currently available agents for the treatment of BK-HC and fluoroquinolone antibiotics are considered as possible prophylactic agents.

Treatment algorithm for BK is as shown **Table 4**.

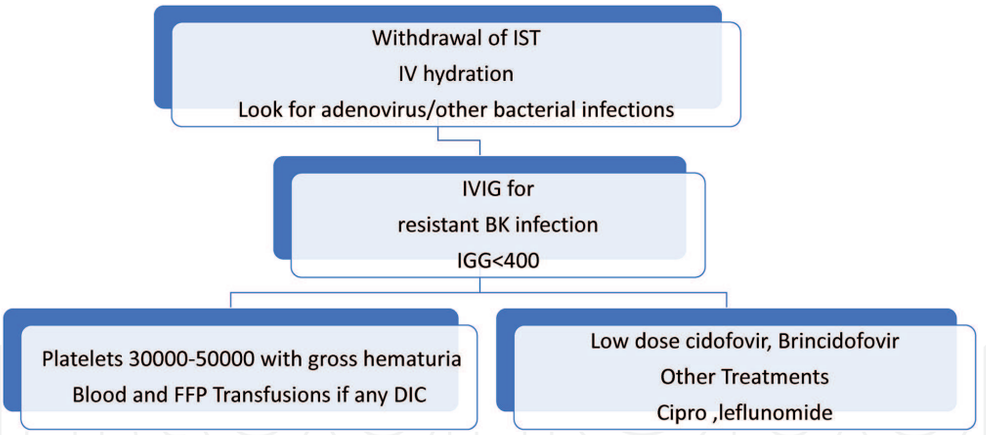

Table 4.
Treatment of BK infection /BK cystitis.

8. HSV/VZV infection: herpesviruses

The herpesvirus group currently consists of eight members, six of which have been implicated as important pathogens in ASCT recipients. During recent years, antiviral agents are used both for prevention and therapy in ASCT patients. Currently available anti-herpesvirus drugs are acyclovir and its prodrug valacyclovir, penciclovir and its prodrug famciclovir, ganciclovir with the prodrug valganciclovir, cidofovir, and foscarnet. All of the available drugs, except foscarnet, are nucleoside analogues and require phosphorylation by viral or cellular enzymes to become activated (**Tables 5** and **6**).

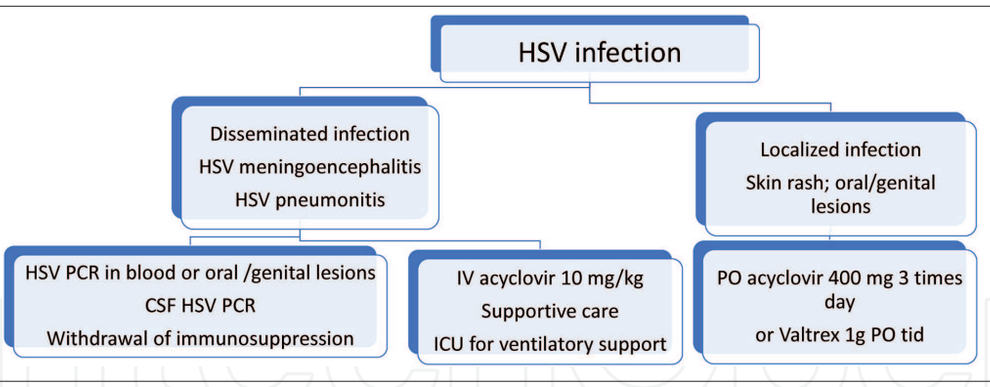

Table 5.
Treatment of HSV infection.

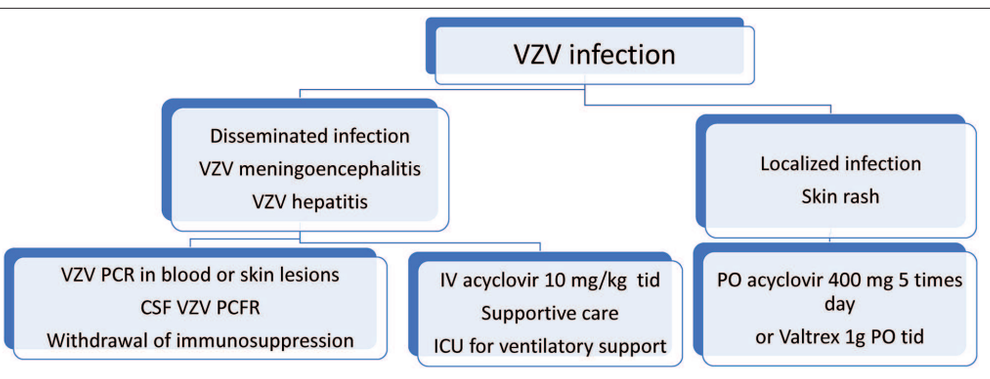

Table 6.
Treatment of VZV infection.

9. Herpes simplex virus (HSV)

The first controlled studies of prophylaxis and therapy of HSV in ASCT patients were performed more than 20 years ago, showing that effective antiviral agents can make an important impact on morbidity and mortality. The results from these early trials showed that acyclovir prophylaxis is indicated in all HSV-seropositive ASCT recipients and in some autologous patients with high risk for mucositis [21]. The duration of antiviral prophylaxis should be adjusted for each individual but should be continued throughout the aplastic phase. A longer duration of prophylaxis should be considered in patients with GVHD or a history of frequent reactivations before transplantation [21]. It is important to realize that HSV reactivations frequently occur quickly after prophylaxis is stopped and might require therapy long-term prophylaxis [22].

Valacyclovir, the prodrug of acyclovir, is also used as prophylaxis but no controlled studies have been performed in transplant patients. Valacyclovir gives similar acyclovir serum levels to IV acyclovir in neutropenic patients. Established HSV disease can be treated either orally or intravenously. The most commonly used drug is acyclovir, which should be given intravenously in patients with disseminated HSV or suspected central nervous system (CNS) disease therapy [22].

The most frequently used agents for HSV prophylaxis and therapy all require the viral enzyme thymidine kinase for activation. Virus resistance occurs with the development of mutant lacking this enzyme. Although acyclovir has been in use for almost 20 years, there has been only a moderate increase in acyclovir-resistant strains of HSV. Recently, acyclovir-resistant HSV have become more common, in unrelated and HLA-mismatched ASCT recipients and in patients who develop GVHD. The recommended drug for acyclovir-resistant HSV has been foscarnet. Currently, the only available antiviral drug available for treatment of double resistant HSV is cidofovir. However, although sensitive *in vitro*, the clinical response in high-risk ASCT patients treated with cidofovir has been variable [22].

10. Varicella-Zoster virus (VZV)

VZV infection is a very severe complication in ASCT patients. The risk is highest in children due to the epidemiologic pattern of infection. The live Varicella vaccine has been shown to be safe in children with acute leukemia but no controlled trial in ASCT recipients has been published and its use is not recommended earlier than 24 months after transplantation. Varicella-zoster immune globulin is the recommended prophylactic measure in seronegative ASCT recipients after an exposure to varicella has occurred if it can be given within 4 days of exposure [21, 22]. Another option is antiviral chemoprophylaxis with acyclovir or valacyclovir but there is no published data regarding the efficacy of this strategy.

11. Prevention of reactivated infection of VZV

The risk of herpes zoster is highest between 3 and 6 months after transplantation. Thus, the duration of antiviral prophylaxis must be long enough to prevent reactivated VZV disease. Two randomized, controlled studies have been performed comparing 6 months of prophylactic acyclovir with place. In addition, a non-controlled study of acyclovir or ganciclovir prophylaxis was recently published. All three studies showed that acyclovir was effective in reducing the risk for herpes zoster during the 6 months of therapy but at 12 months after transplantation there

was no longer any difference. An unpublished study by Bowden and colleagues from the Seattle group indicated that the rebound in VZV disease does not occur if the prophylaxis is prolonged to 12 months [23]. Valacyclovir has not been studied for VZV prophylaxis, but the rate of VZV disease was reduced in a study when valacyclovir was compared to acyclovir as CMV prophylaxis. Some centers, however, do use valacyclovir as long-term prophylaxis against VZV [21, 22].

12. Treatment of VZV disease

The recommended therapy for a primary varicella or disseminated herpes zoster is intravenous acyclovir 10 mg/kg (or 500 mg/m^2) three times daily. For localized dermatomal herpes zoster, oral acyclovir 800 mg given five times daily was compared with IV acyclovir in a small randomized study in ASCT patients and the outcome was comparable. Famciclovir 500 mg given three times daily was compared with acyclovir 800 mg five times daily in ASCT, solid organ transplant and oncology patients, and the results indicated similar efficacy. No controlled study has been performed with valacyclovir given for treatment of a herpes zoster in ASCT patients. VZV resistance to acyclovir is rare but has been reported after ASCT [22, 23].

Treatment algorithm for HSV/VZV is as shown in **Tables 5** and **6**.

13. Other upper respiratory infections

The conditioning regimen has an impact on the incidence of these infections. Even though the patients with myeloablative and non-myeloablative conditioning have similar incidences for respiratory viral infections, LRI are significantly increased during the early post myeloablative ASCT period compared to non-myeloablative ASCT [14, 15].

14. Treatment of respiratory viral infections post ASCT

Lower overall survival seen with respiratory virus infection is due to bacterial co-infection causing increased mortality in high-risk patients with lymphopenia, CMV DNAemia at the time of viral LRI and need for oxygen support. Over the past years, more respiratory infections in ASCT recipients have been reported due to the use of new multiplex polymerase chain reaction (PCR) tests with higher sensitivity, specificity compared to conventional viral culture and antibody assays. Early diagnosis and treatment are important to improve outcomes of patients with upper respiratory viral infections (URI) s and lower respiratory viral infections (LRI)s [14, 15].

15. CMV-specific T cell lines and multi virus-specific T cell lines (multi-VST)

Immunotherapeutic strategies to hasten T cell recovery after ASCT remain an option as an adjunct to drug treatments. CMV-seropositive patients who are recipients of T cell-depleted CMV-seronegative donor or cord blood grafts are at highest risk from CMV-associated morbidity and mortality. Severe GVHD and drug-induced T cell dysfunction are also risk factors for CMV-related morbidity.

Recovery of CMV-specific CD4 responses is critical to effective antiviral responses, and restoration of both antigen-specific CD4 and CD8 T cell populations to control CMV is critical in this scenario [14–16].

An alternative to CMV-specific T cell clones is the use of CMV-specific T cell lines. In a clinical study, a single infusion of CMV-specific CD4 T cells showed plasma CMV clearance in 63% of patients. The HLA-A2–restricted pp65 peptide NLVPMVATV (NLV) is also being used but a major disadvantage of the HLA-A2–restricted NLV peptide approach is the restriction of benefit to HLA-$A2^+$ patients only [10, 16, 17].

Multi-VST lines represent an interesting option to target multiple viral infections using adoptive cell therapy. Such lines can be manufactured either with APC systems using overlapping peptide pools from multiple viruses, or with other gene transfer approaches by the use of an adenoviral vector encoding the CMV-associated pp65 antigen to transduce APCs (MoDCs and EBV-transformed lymphoblastoid cell lines [LCLs]) before coculture with PBMCs or naive cord blood. This method delivers both MHC class I-dependent processing and expansion of CMV-reactive CD8 T cells, and MHC class II-dependent processing and presentation of adenovirus/EBV/CMV-associated peptides to drive expansion of virus-specific CD4 T cells. The adenoviral transfer vector promotes anti-adenoviral T cell specificity (bispecific CTLs), and if EBV-transformed B cells are used in lieu of MoDCs, then additional EBV-specificity is generated (trispecific CTLs) [10, 16, 17].

Trispecific CTLs administered prophylactically has demonstrated CMV-specific reactivity in 70% of patients with no increase in the incidence of GVHD. CMV- and EBV-specific T cell numbers rise in the absence of viral reactivation, but adenoviral-CTL expansion is only observed in the context of adenoviral infection. More recent studies have used nucleofection to introduce DNA plasmids encoding multiple immunogenic antigens from CMV, EBV, and adenovirus into APCs, or have used viral antigen–derived 15-mer peptide libraries (pepmix) with APCs to deliver a product with a broader CMV-reactive T cell repertoire [10, 16, 17].

16. Conclusion

Increased numbers of both systemic and upper respiratory tract viral infections occur post-transplant due to ineffective immune reconstitution. Early diagnosis and treatment are critically important to reduce morbidity and mortality associated with these infections. Viral infections cause morbidity and mortality in these immunosuppressed patients due to inability of the host immune system to limit viral replication and dissemination, and loss of T cell function is central to this effect. Immunotherapeutic strategies to accelerate reconstitution of virus-specific immunity and to hasten T cell recovery after transplants remain a compelling alternative to drug treatments. CMV- and EBV-directed virus-specific T cells (VSTs) are being used in the settings of profound immunosuppressed SOT and ASCT patients. Emerging evidence supports the use of VSTs for treatment of broader range of viral targets, including varicella-zoster virus, adenovirus, and BK virus [10, 14–17].

Abbreviation

EBV	Epstein Barr Virus
PTLD	post-transplant Lymphoproliferative disorder
IST	immunosuppression
HHV6	human Herpes simplex virus 6

BK	BK polyoma virus
HSV	Herpes simplex virus
VZV	Varicella Zoster virus
PCR	polymerase chain reaction
CSF	cerebrospinal fluid
IVIG	intravenous immunoglobulin

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