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Review

Viral Infections in Allogeneic Hematopoietic Stem Cell Transplant Recipients: Literature Review

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Abstract

Hematopoietic stem cell transplant (HSCT) recipients are at an increased risk of bacterial, viral, fungal and parasitic infections. Past exposures to infections, the degree of immunosuppression, prolonged neutropenia and presence of graft versus host disease (GVHD) are some of the factors which make HSCT recipients more susceptible to infections. Viral infections have emerged as a major challenge causing high morbidity and mortality in stem cell transplant recipients. Myeloablative conditioning regimens and GVHD prevention strategies which may delay immune reconstitution and serologic status of donors and recipients affect the incidence of viral infections. Community-acquired respiratory and gastrointestinal viral infections like respiratory syncytial virus (RSV), rhinovirus, adenovirus, influenza, norovirus and reactivation of latent viruses like herpes simplex virus (HSV), cytomegalovirus (CMV) are some of the important pathogens increasing the morbidity and mortality in transplant recipients. Clinical manifestations range from asymptomatic carriage to severe disease. Due to lack of effective agents to treat viral infections and emerging resistance patterns, preventive and prophylactic strategies are valuable. Our review article

provides an overview of commonly encountered viral infections and their management in an allogeneic stem cell transplant setting in the adult age group.

Keywords
Viral infections; allogeneic stem cell transplants; hematopoietic stem cell transplants

1. Introduction

Viral infections can be asymptomatic or subclinical or even lead to severe disease in allogeneic HSCT recipients. Viral diseases of importance in HSCT include herpes simplex virus (HSV), varicella-zoster virus (VZV), human herpesvirus 6 (HHV-6), cytomegalovirus (CMV), Epstein-Barr virus (EBV) and respiratory viruses (eg, respiratory syncytial virus, adenovirus, influenza, parainfluenza). Most of these viral infections are opportunistic in nature and are related to factors influencing engraftment and immune reconstitution [1]. Increase in HLA mismatched donor allogeneic transplants and using anti-thymocyte globulin (ATG) for GVHD prevention are few factors which predispose recipients to viral infections [2, 3]. Fortunately, based on molecular diagnostic methods, a polymerase chain reaction can offer an early diagnosis of these infections [4, 5]. Early diagnosis facilitates timely intervention controlling infection associated complications. Many prophylactic and pre-emptive treatment strategies are also aimed at decreasing viral infection-related complications [6]. Immunotherapy to restore virus-specific immunity are proven to be effective in treating CMV, EBV and adenovirus infections [7]. In our review article, we have made an attempt to discuss risk factors for post-HSCT viral infections, preventive strategies and treatment options.

2. Risk Factors for Viral Infections

2.1 Source of Stem Cells

Peripheral blood stem cells achieve faster hematopoietic and immune reconstitution compared to bone marrow and cord blood source. Hence, this is associated with fewer incidences of viral infections [8, 9].

2.2 Donor and Patient Characteristics

Serology status of donors and recipients affects the incidence of viral infections. For example, if a donor is CMV seronegative, then a CMV seropositive recipient is at a very high risk of CMV reactivation [10]. Similarly, previous recipient exposure to VZV, HSV and EBV pose a higher risk of reactivation during immunosuppression. Anti-viral prophylaxis and pre-emptive therapy can be given to avoid these complications [11]. Older age group and multiple lines of chemotherapy prior to HSCT also increase the risk of viral infections.

2.3 Degree of HLA (Human Leukocyte Antigen) Match

An increased risk of viral infections is noted in HLA- mismatch related and unrelated transplantation compared to HLA-match related transplantation. This is secondary to delayed

immune reconstitution because of more intensive GVHD prophylactic strategies such as the use of ATG [1, 12].

2.4 Conditioning Regimens and GVHD

Myeloablative conditioning regimens typically render the recipient neutropenic for weeks and also cause more mucosal damage increasing the predisposition for viral infections in the immediate post-transplant period. Non-myeloablative regimens have variable engraftment periods and lesser incidence of mucositis. Hence, in the immediate post-transplant period the incidence of infection is less [1]. Kim et al demonstrated that overall incidence of bacteremia is low in non-myeloablative transplants than in myeloablative transplants [13]. However, the rates of occurrence of viral and invasive fungal infections were similar in both myeloablative and non-myeloablative transplant groups [13]. Although, the degree of myelosuppression is milder in non-myeloablative conditioning, the extent of lymphodepletion is similar in both conditioning strategies. Schulenburg et al reported significant differences in the immunological recovery of myeloablative and non-myeloablative transplant recipients [14]. This study showed a higher number of infections in the first 30 days in patients who underwent a myeloablative transplant however, the risk of viral infection was the same in both myeloablative and non-myeloablative groups [14]. Restoration of humoral immune competence may be delayed due to the development of GVHD and the recipients are predisposed to viral infections for almost upto a year [11]. GVHD and its treatment is an independent risk factor for viral infections [15].

Profound T cell depletion for GVHD prophylaxis has been associated with a higher incidence of disease relapse as well as viral infections as shown in various studies [16, 17].

3. Timeline of Viral Infections

Time elapsed since transplant can be classified into 3 phases. The pre-engraftment phase which is from stem cell infusion to approximately day 30. Immediate post-engraftment phase from engraftment to day 100 and late post-engraftment phase after day 100 [18]. Allogeneic HSCT recipients are at risk of infection in all 3 periods. A study by Srinivasan et al showed that in the pre-engraftment period HSV and RSV infections were more commonly seen compared to CMV, EBV or Adenovirus. CMV reactivation was more common than HSV or EBV in the immediate post-engraftment period. In the late engraftment period, there was no statistically significant distribution between HSV, CMV, EBV or Adenoviral infections [18]. BK virus-associated hemorrhagic cystitis is commonly seen in the immediate and late post-engraftment period. Hemorrhagic cystitis in pre-engraftment phase is usually drug induced. VZV, HHV-6, EBV, and CMV are more common in immediate and late post engraftment periods [19-21].

3.1 Herpes Simplex Virus

All HSCT candidates undergo testing for anti-HSV IgG before transplant. Type-specific HSV testing is not required [11]. Almost 90% of adults are HSV seropositive with one or both serotypes. HSV1 is more prevalent affecting 50 to 65% of population [22]. HSV2 infections are less frequent and there are broad regional variations [22]. Overall prevalence of HSV2 infection ranges from 10 to 60% [23]. Seronegative patients are informed to avoid exposure to HSV infection while

immunocompromised. Patients with primary, disseminated and severe mucocutaneous HSV infections are placed under contact precautions. Visitors to HSCT center with active HSV infection are not allowed to come in contact with HSCT recipients.

Without prophylaxis, allogeneic HSCT patients who are seropositive are at an 80% risk of reactivation especially during the first 4 weeks of transplantation [24, 25]. With the use of acyclovir prophylaxis, this has decreased to 0 to 3% [24, 26]. Seropositive patients are given acyclovir prophylaxis starting on the day of conditioning up to day 30 (until engraftment or resolution of mucositis). The recommended oral dosage is 400 to 800mg twice daily. In patients with recurrent HSV infections or risk of Varicella zoster disease duration of prophylaxis is increased to 1-year post-HSCT [19]. For long term prophylaxis, a higher dose (800mg twice daily) is recommended to minimize resistance and for maximum viral suppression. Patients with poor oral absorption can take intravenous (IV) Acyclovir 250mg/m2 /dose 12 hourly [11, 27]. Ganciclovir has in-vitro activity against HSV 1 and 2. Acyclovir should be discontinued in patients receiving Ganciclovir for CMV prophylaxis or treatment [28, 29]. HSV prophylaxis is not indicated in seronegative recipients receiving stem cells from an HSV seropositive donor [11]. Valacyclovir has better oral bioavailability and is equally effective as HSV prophylaxis. The oral dose is 500mg twice daily. Caution is advised in renal failure especially when being used in post-engraftment phase [27, 30]. Not enough data is available regarding the usage of famciclovir prophylaxis in HSCT patients [11].

Acyclovir-resistant HSV disease is rare. Resistance occurs due to a reduced activity or mutations of viral thymidine kinase resulting in reduced activation of acyclovir in infected cells. Prolonged use of low dose acyclovir is also one of the causative factors [31]. Foscarnet is recommended in acyclovir resistance. Induction dose is IV 40 mg/kg/dose every 8 to 12 hours for 14 to 21 days. Routine prophylaxis with foscarnet is not recommended due to substantial renal and infusion-related toxicity [11]. Cidofovir may be used in cases resistant to both acyclovir and foscarnet, however, the data is limited [32].

Few case reports have been published citing successful clearance of HSV in acyclovir resistant cases [33, 34]. Lee et al reported a retrospective review of 30 HSCT patients who received brincidofovir prophylaxis for cytomegalovirus, adenovirus and treatment for acyclovir resistant disease [35]. Overall breakthrough rate of HSV infection was 1 per 1000 patient days demonstrating potential efficacy of brincidofovir prophylaxis against HSV [35]. More studies are needed to determine the indications, efficacy and feasibility of using brincidofovir as HSV prophylaxis.

3.2 Varicella-Zoster Virus

Primary VZV infection which most commonly occurs in childhood causes Varicella after which the virus becomes dormant in the dorsal root ganglia of immunocompetent hosts. Reactivation of VZV causes herpes zoster [1]. All HSCT candidates should be tested for VZV IgG antibodies. VZV susceptible close contacts of immunocompromised HSCT recipients should be vaccinated at least 4 to 6 weeks before transplant dates [11]. Vaccine recipients who develop a rash post vaccination should avoid contact with immunocompromised patients [11]. Transplant recipients who develop dermatomal zoster should be kept under strict contact and airborne precautions ideally 8 days

after exposure to VZV and continued until 21 days after last exposure or until all skin lesions have crusted [36].

Acyclovir prophylaxis is recommended for at least 1 year after HSCT. This regimen is most effective in preventing VZV reactivation [19, 37]. In patients with chronic GVHD and on immunosuppressive drugs, acyclovir prophylaxis should be continued. There are no clear cut guidelines regarding the duration of prophylaxis as there is a persistent risk of reactivation despite being on prophylaxis [38]. Some authors recommend that it is worthwhile to continue acyclovir prophylaxis until 6 months after discontinuing immunosuppressive drugs [11]. Valacyclovir is a prodrug of acyclovir and has better oral bioavailability.

This can be safely used in severely immunocompromised patients [39]. There is no data on the usage of famciclovir in HSCT recipients. VZV resistance to acyclovir is rare. However, when suspected or virologically documented, foscarnet is recommended for pre-emptive therapy [40]. Oral brivudin and famciclovir have also proven effective [41, 42]. In case of VZV like rash in HSCT recipients undergoing conditioning, IV acyclovir should be administered until 48 hours after all the lesions are crusted and treatment may be completed with oral valacyclovir [11].

3.2.1 Indications for Varicella Zoster Immunoglobulin (VZIG)

VZIG should be given to all VZV seronegative HSCT recipients less than 2 years of HSCT or more than 2 years of HSCT on immunosuppression or having chronic GVHD who come in close contact with a person having chickenpox or shingles no later than 96 hours of exposure [11]. Where unavailable, acyclovir or valacyclovir alone can be administered [43, 44]. Patients undergoing conditioning therapy who are exposed to a recent vaccine recipient with a varicella-like rash should also be given one of the 3 agents. If these patients are re-exposed to varicella more than 3 weeks after receiving VZIG, they should be re-immunized by another dose of VZIG or one more course of valacyclovir [11, 45]. VZV seropositive HSCT patients who are immunocompromised due to conditioning chemotherapy, chronic GVHD or high dose steroid treatment should receive VZIG and acyclovir or valacyclovir after exposure to varicella or varicella-like rash in a vaccine recipient [43].

3.2.2 Vaccinations

There are 2 live varicella vaccines against VZV. One is directed against chickenpox and the other against shingles. Both are live vaccines. The chickenpox vaccine has low viral titers and can be used in varicella – seronegative HSCT recipients who do not have active GVHD and are not receiving immunosuppression. The vaccine should be given ≥24 months following transplantation [11, 46].

Live zoster vaccine is not recommended to be given to HSCT recipients due to high viral titers [11]. Recently a recombinant zoster vaccine (RZV) (Shingrix) has been approved in immunocompetent adults more than 50 years of age, 2 doses are given 6 months apart [47]. This vaccine is given only to varicella seropositive patients. No formal recommendations are available for HSCT recipients [48].

A phase I/II study in 121 autologous stem cell transplant patients showed a good humoral and cellular immunity when RZV was given 2, 3 and 5 months post autologous transplant. Adverse reactions were of mild to moderate intensity and immunization did not affect disease relapse or

graft failure [49]. Results from a phase III randomized control study in autologous transplant patients and renal transplant patients are awaited [48]. Although there are no formal studies in HSCT recipients, an earlier study on VZV glycoproteins has indicated a potential clinical efficacy [50].

3.3 Human Herpes Virus 6 and 8

Human Herpes Virus 6 (HHV6) causes roseola or sixth disease in children. Reactivation in pediatric HSCT recipients has been known to cause acute limbic encephalitis, hepatitis, fever, rash, pulmonary syndrome. Ganciclovir, Foscarnet, and Cidofovir have been found to have in-vitro activity against HHV-6 [51-54]. In adults, HHV6 reactivation is associated with delayed engraftment, bone marrow suppression and acute pneumonitis and may be associated with increased mortality [55, 56]

Human Herpes Virus 8 (HHV8) can cause Kaposi's sarcoma (KS). This occurs rarely after HSCT [57]. More commonly these can be seen in solid transplant recipients. It can also present as intra-cavitary primary effusion lymphoma or multicentric Castleman disease [58]. It is associated with cytopenias in disseminated disease and carries a mortality rate of 8 to 14% [58]. Diagnosis is confirmed by histopathology and demonstrating HHV8 immunohistochemically. Cytotoxic chemotherapy, surgical excision, and radiation are the mainstay of treatment [59]. Antiviral drugs including cidofovir, ganciclovir, and foscarnet have been used to decrease the viral load and to contribute to better control of disease [60-62].

3.4 Cytomegalovirus (CMV)

HSCT recipients and donors are screened for CMV IgG antibodies to determine the risk for primary CMV infection and reactivation. HSCT recipients who are CMV seropositive and seronegative patients who have received stem cells from a seropositive donor are at risk of reactivation. To reduce the risk of infection, CMV safe leucocyte-depleted blood products are used [63, 64]. Generally, CMV can be detected in blood in asymptomatic patients, one to two weeks before CMV disease. A pre-emptive approach includes weekly monitoring of CMV titers by quantitative PCR in whole blood and treating patients who develop viremia [11]. The initial CMV viral load and the rate of increase in titers correlate with the risk of developing CMV disease [65]. CMV can cause multi-organ disease including pneumonia, gastroenteritis, hepatitis, retinitis, and encephalopathy. The gold standard for diagnosing tissue invasive disease is by demonstrating CMV inclusion bodies or CMV positive immunohistochemical staining on histopathology.

HSCT patients will be receiving acyclovir or valacyclovir as herpes prophylaxis. High dose valacyclovir prophylaxis (2 grams 4 times a day) has shown a reduction in CMV infection [39]. CMV titers are monitored weekly starting from day +7 to day 100 in all HSCT recipients. In patients with CMV infection early in transplant, cord blood transplant and CMV negative recipients with CMV positive donors on immunosuppression due to chronic GVHD weekly titers are monitored up to 365 days. There is no consensus as to when pre-emptive therapy should be initiated. Some studies suggest a threshold level of 500 copies/mL and others 1000 copies/mL [65-68]. In our center, we follow a threshold of 1000 copies/mL to initiate pre-emptive treatment.

Ganciclovir is the first-line drug which has shown a significant reduction in the risk of CMV disease [69]. Oral valganciclovir can also be used in pre-emptive therapy with frequent monitoring

to prevent cytopenias. Treatment is continued until the CMV viral load is negative for a minimum of 2 weeks. Resistant infection should be suspected when CMV viremia does not improve and titers continue to increase despite appropriately dosed and delivered antiviral treatment [70]. Risk factors for developing resistance include previous anti-CMV drug exposure for a prolonged duration, inadequate dosing, bioavailability or absorption, profound immunosuppression, and corticosteroids usage. In drug-naïve patients, there might be a modest increase in viral load during the early phase of treatment because of immunosuppression and steroid use, this should not be labelled as clinical resistance and does not necessitate therapy change [71]. The incidence of CMV resistance has been reported to be around 14.5% [72]. Resistance testing is done to identify specific resistance mutations using automated sequencing methods. This can be done in plasma, cerebrospinal fluid or bronchoalveolar lavage and requires a viral load of 1000 copies/Ml [73]. UL54 mutation confers multidrug resistance to ganciclovir, foscarnet and/or cidofovir. UL97 mutations confer resistance to ganciclovir and valganciclovir [70].

If viremia is not improving despite 2 weeks of ganciclovir or valganciclovir therapy or there is evidence of CMV end-organ disease with more than 6 weeks of therapy, it is recommended to switch to foscarnet and reduce immunosuppression if possible. Genotypic analysis to detect resistant mutations is required [70]. Pre-hydration and electrolyte monitoring should be done in patients receiving foscarnet to prevent nephrotoxicity. In case of UL97 mutation in the absence of CMV end-organ disease, if there is less than 5 fold ganciclovir resistance, dose escalation to 10mg/kg twice daily has been found to be beneficial [74]. Some centers use this approach along with the continuation of a half dose of foscarnet [70]. Single-agent foscarnet is the drug of choice in the presence UL97 mutations which show 5 fold increase in ganciclovir resistance [70]. Cidofovir has a potent anti CMV activity and is not affected by UL97 mutation. Due to toxicity and limited experience in HSCT recipients no recommendations are found [70, 75].

UL54 mutations occur within the cluster of conserved regions of homology (exonuclease domains I through III and polymerization domains I through III) thus conferring various patterns of cross-resistance among the antiviral drugs [70]. Based on the pattern of cross resistance therapy needs to be tailored. In case of ganciclovir-foscarnet –cidofovir cross resistance, one of the approaches to treatment is to continue foscarnet and add high dose ganciclovir (10mg/kg twice daily) and add leflunomide as an adjunct therapy. In case of toxicities or lack of response, switching to investigational drugs is recommended [70].

3.4.1 Anti-CMV Novel Agents

Maribavir is a benzimidazole antiviral which has in vitro activity against CMV strains resistant to ganciclovir, foscarnet, and cidofovir [76]. Maribavir inhibits UL97- mediated phosphorylation and has anti-CMV effects on CMV DNA synthesis. Phase 1 data showed a favorable safety profile for doses up to 2400mg/day [77]. A phase 2 trial showed positive results for CMV prophylaxis at a higher dose of 400mg twice daily [78]. However, prophylaxis with 100mg twice daily of maribavir failed to prevent CMV in HSCT recipients [78]. A recent randomized phase 2 study has shown that maribavir in dosages ≥400mg twice daily was active against refractory or resistant CMV infections in HSCT and solid organ transplant recipients [79]. It is important to note that as maribavir inhibits UL97, it impairs phosphorylation of ganciclovir hence these two drugs should not be given together [80].

Brincidofovir is an oral lipid conjugate of cidofovir which has a higher potency and is less nephrotoxic [81]. It acts by inhibiting pUL54. Gastrointestinal toxicity, predominantly diarrhea is the main adverse effect [82]. Brincidofovir can be utilized in infections resistant to ganciclovir. Although several case series have shown encouraging results [34, 83], a phase III study failed to demonstrate the efficacy of Brincidofovir in the prevention of clinically significant CMV infections in HSCT patients [84].

Letermovir's (LMV) antiviral activity is highly specific to CMV. It acts by inhibiting the terminal phase of the virus life cycle by targeting UL56 of the terminal complex enzyme [85]. This has activity against viruses resistant to other antiviral molecules. There is no cross-resistance reported due to its unique mechanism of action [86]. Primary resistance to this molecule is rare to non-existent [87, 88]. A phase III study confirmed that prophylactic LMV (480 mg/day, decreased to 240 mg/day when co-administered with cyclosporine) resulted in a significant reduction in the number of CMV infections at end of treatment and 10 weeks later with a significant reduction in mortality and satisfactory tolerability [89]. This study also demonstrated an overall survival benefit at 24 weeks although the benefit was lost at 48 weeks [89]. LMV has a low barrier to resistance and does not have cross-activity against other viruses including HSV [90]. Letermovir has been approved for primary and secondary CMV prophylaxis in Canada and USA [91].

3.4.2 CMV specific Cytotoxic T Lymphocytes (CTL)

Cellular adoptive immunotherapy has been used in CMV infections not responding to antiviral treatment with good results [92]. It is recommended to use CTL as an adjunct to antiviral treatment [70]. Logistical difficulties like cost, availability, limited use in patients on high dose steroids for GVHD and time to generate adequate cells for infusion pose challenges in CTL usage [70]. Multiple infusions may be required if there is a suboptimal response or rebound viremia. Rarely donor-derived CTL infusion can cause graft failure and transfusion-associated microangiopathy [93].

3.4.3 Other Therapies

Using CMV intravenous immunoglobulins as an adjunct therapy is controversial due to lack of data [70]. Leflunomide has in-vitro activity against ganciclovir-resistant CMV and has been used as an adjunct with other antivirals to treat refractory CMV infections with variable results [94, 95]. Artesunate has been used in a few cases with variable success. It has in-vitro activity against ganciclovir-resistant CMV. Some centers use this as an adjunct treatment when everything else has failed [96, 97].

3.5 Epstein Barr Virus (EBV)

HSCT donors and patients are screened for anti-EBV IgG antibody to determine the risk for primary EBV infection post-transplantation. In HSCT patients, EBV disease occurs due to reactivation of endogenous infection or transmission from the graft [98]. The most significant clinical manifestation of EBV disease is post-transplant lymphoproliferative disorder (PTLD) [99]. The incidence of PTLD is around 3.2% in HSCT recipients with higher numbers occurring in mismatched unrelated donor transplants [100]. Interestingly, haplo-identical transplants using

post-transplant cyclophosphamide (PT-Cy) had a low incidence of PTLD [101]. The median time to development of PTLD is around 2 to 4 months [100, 102]. PTLD can also occur after 1 year of transplant in about 4% of cases [100].

Risk factor for EBV disease is T cell depletion or impairment as seen in cord blood transplants or regimens that use ATG or alemtuzumab. Patients undergoing autologous transplants are regarded as low-risk cases to develop EBV disease. Patients undergoing haplo transplant with PT-Cy have intermediate risk and patients undergoing matched or mismatched unrelated donor transplant have a high risk of developing EBV disease [103]. EBV matched donor is recommended to reduce the risk of EBV disease [103]. EBV viral load monitoring with a quantitative PCR should begin within one month of HSCT and should continue weekly for at least 4 months [103]. Longer monitoring is recommended in patients who are considered to have poor T cell reconstitution Eg: patients with acute or chronic GVHD, ATG or alemtuzumab-based conditioning regimens and inpatient who have early EBV reactivation [103]. Fever and lymphadenopathy are the presenting features and diagnosis should be confirmed by a biopsy whenever possible. If tissue diagnosis is not possible, then combined quantitative PCR and PET CT scan findings are acceptable to diagnose EBV disease [102, 104, 105].

Latently infected B cells do not express EBV thymidine kinase protein, hence antiviral treatment has been unsuccessful despite in vitro activity of acyclovir, ganciclovir, foscarnet, and cidofovir against EBV [106]. Prophylactic use of rituximab is limited to patients with the highest risk of EBV-PTLD. Care should be taken to monitor closely for infections and hypogammaglobulinemia. Intravenous immunoglobulins (IVIG) can be given in case of hypogammaglobulinemia and recurrent infections [103, 107]. EBV specific CTLs are highly efficacious as prophylaxis against EBV –PTLD in high-risk cases, however, due to cost and resources; it is available only in selected centers [108]. The initial management of PTLD includes restoration of immune response to EBV by reducing immunosuppression [109, 110].This strategy is difficult and may not be useful in early phase of transplant as immune- reconsitution may not be fast enough to eradicate the malignant cells [109]. In later phases with partial immune recovery, decreasing immune suppression may alone be enough to treat EBV PTLD in early stages [111]. This can also be employed as a prophylactic strategy in patients with rising EBV DNA levels without any evidence of lymphoma [109, 112]. Calcineurin inhibitors must be reduced by atleast 50% and antimetabolites such as mycophenolate mofetil must be discontinued where feasible [110].

Pre-emptive therapy is recommended in patients with significant EBV PCR viral load without symptoms or disease in patients with a high risk of EBV-PTLD. Treatment is given until the EBV PCR levels are below the initial threshold [103]. Due to the variability of PCR techniques a specific threshold to initiate pre-emptive therapy is not recommended [11]. Some authors recommend a threshold of 10,000 copies/mL in plasma [113, 114]. The rate of increase in EBV copies is clinically significant in guiding treatment [103]. Rituximab at 375 mg/m2 is given once weekly until EBV PCR negativity. The number of doses is determined based on response and tolerability of the patient. Typically 1 to 4 doses are sufficient [103]. When possible immunosuppression should be reduced and donor or third party EBV specific CTLs should be infused for efficient control of EBV viremia [103]. In EBV-PTLD reduction of immunosuppression alone is not beneficial and increased the risk of GVHD [115]. Early treatment with weekly rituximab monotherapy for up to 4 weeks along with EBV viral load monitoring is associated with a positive outcome in about 70% of patients [103]. A number of rituximab doses may downregulate CD20 expression and decrease efficacy [103].

Response to treatment is determined by at least 1 log10 reduction in viral load in the first week of treatment and disappearance of signs and symptoms of PTLD [100]. In the case of rituximab failure, second-line treatment options are EBV positive donor lymphocyte infusions (DLI) to restore T cell reactivity [116, 117] or EBV specific CTLs [118, 119]. Donor or 3rd party derived CTLs are the preferred second-line treatment due to the high risk of GVHD associated with DLIs. Chemotherapy is reserved for relapsed – refractory EBV PTLDs due to the risk of neutropenia, graft failure and poor tolerability [103].

Management of central nervous system (CNS) PTLDs is difficult due to unsuccessful eradication of EBV infected B cells from CNS [103]. Possible therapeutic options include methotrexate and cytarabine-based primary CNS lymphoma chemotherapy protocols [120], radiotherapy, intrathecal rituximab [121], T cell therapy with EBV specific CTLs [122].

3.6 Virus Specific CTLs

In cases of refractory viral infections and where effective antiviral agents are not available for treatment, strategies for early T cell reconstitution are required for effective treatment of these viral infections [123]. Predominantly CMV, EBV in adults and Adenovirus in children are responsible for refractory infections [124]. Overall treatment response is around 60 to 80% with conventional pharmacotherapy [124]. In adenoviral infections, mortality benefit from preemptive therapy is inconsistent [125, 126]. Antiviral drugs have a significant side effect profile and also require immune reconstitution which is difficult in early phases of transplant. For these reasons, newer treatment strategies are the need of the hour. Use of seropositive donor lymphocyte infusions (DLI) is an effective salvage therapy. This was initially tried in EBV PTLD with good response [116]. However, the risk of severe GVHD limited the use of DLIs. Virus specific (VS) CTLs either third party or donor derived are being manufactured minimizing allo-reactive T cells in the final product. Defined immunogenic antigens which are identified by epitope mapping are presented using an antigen presenting cell such as monocytes, B cells, fibroblasts or artificial K562 based cells. These express major histocompatibility complex antigens to present virus antigen derived peptides and costimulatory molecules which induce T cell activation and expansion [123]. For better availability of virus specific CTLs rapid manufacturing techniques including using third party T cells are being developed [118, 123]. Ex-vivo stimulation and expansion requires a small volume of blood. Thus expanded CTLs may theoretically cause GVHD due to cross reactivity however, no studies have reported an increase in acute or chronic GVHD [123].

In vivo expansion of virus specific CTLs was seen after a single infusion which resulted in persistent clearance of viral antigenemia [127, 128]. Most methods generate varied levels of CD4 and CD8 T cells and this polyclonal phenotype helps persistence of VS CTLs in vivo [128].

EBV PTLD managed with rituximab shows an overall survival of 46 to 67% at one year and overall response rates of 60% in various studies [129-131]. Approximately 50% of them had progression within 6 months of completion of therapy [130]. Heslop et al studied 114 patients between 1993 and 2005, who received EBV specific CTLs to prevent or treat EBV PTLD. None of the 101 patients who received CTL developed PTLD and 11 out of 13 patients treated for PTLD sustained complete remissions. This study showed that adoptive immune therapy is 80% effective when used for treating PTLD and 100% effective when used as preemptive therapy [108].

The efficacy of preemptive therapy in CMV has been shown in several trials. Goodrich et al showed 80% response rates and significant increase in overall survival with ganciclovir [132]. A French cohort showed ganciclovir resistance in 5.2% of patients and was associated with poorer outcome [133]. The overall incidence of CMV resistance is around 14% [72]. CMV specific CTLs will be useful in refractory and resistant cases. Numerous clinical trials have demonstrated efficacy of CMV specific CTL therapy [92, 134]. Similarly, adenovirus specific T cells are proven to be efficacious in treating advanced disease [135, 136].

3.7 Respiratory Viruses

The incidence of infections due to respiratory viruses in transplant patients is similar to the normal population. However, the immunocompromised state leads to prolonged viral shedding, progression to viral pneumonia and increased mortality [137]. Respiratory syncytial virus (RSV), influenza and parainfluenza virus, metapneumovirus are commonly encountered and the effects are well documented. Less information is available on human rhinovirus, bocavirus and human coronavirus [138]. In symptomatic patients, a nasal swab sample for multiplex viral polymerase chain reaction (PCR) is the preferred method to diagnose viral infections [138]. It is not recommended to test asymptomatic donors [11]. Proper droplet isolation precautions are required to avoid the transmission of viral infection to other HSCT patients and to health care workers. It is recommended to postpone conditioning chemotherapy in HSCT patients with an upper respiratory infection (URI), as it can progress to lower respiratory infection (LRI) during immunosuppression [139, 140].

It is important to determine the etiology of URI as RSV, influenza and parainfluenza viruses can progress to more serious LRI and certain viral infections can be treated [11]. All HSCT candidates and their close contacts should receive seasonal influenza vaccine every year. If there is an outbreak with an influenza strain not covered by the vaccine, all HSCT candidates and their close contacts and health care workers involved in the care of HSCT recipients should receive chemoprophylaxis for approximately 2 weeks with an agent active against the circulating influenza strain like neuraminidase inhibitors [11, 141]. Neuraminidase inhibitors are the first line agents for the treatment of influenza [142, 143]. Clinical outcomes are similar between using IV peramivir and oral oseltamivir [144]. However, in cases of mutations causing resistance (H275Y in H1N1) to these 2 drugs, inhaled zanamivir is used [145]. Another oral drug baloxavir marboxil has been recently approved for use in oseltamivir-resistant cases [146] In severe influenza infections, a triple combination therapy including oseltamivir, ribavirin, and amantadine has been tried successfully [147].

In cases of parainfluenza, there was no impact of ribavirin on the symptom, viral shedding, and progression to LRTI or mortality [148, 149]. Although, some centers did use aerosolized ribavirin and demonstrated a moderate reduction in overall mortality [150]. For RSV infections, various pre-emptive therapy strategies have been proposed including systemic ribavirin [151], RSV immunoglobulins in combination with aerosolized ribavirin [152] and RSV monoclonal antibody-palivizumab [153].

One-third of HSCT recipients with human metapneumovirus infection can progress to pneumonia [154]. Ribavirin's role in treating metapneumovirus infection is unknown and no recommendations are available [11]. There are few case series reporting successful treatment of

metapneumovirus pneumonia with ribavirin and intravenous immunoglobulin combination [155].There are no directed therapies recommended in bocavirus, coronavirus and rhinovirus infections [138].

3.8 Adenovirus

Adenovirus infections are either acquired or can be a result of reactivation. However, pre-transplant donor and recipient screening are not recommended. Cellular immune responses are cross-reactive among different serotypes. This provides long term immunity against reactivation and serious infections are uncommon. Universal droplet and isolation precautions are practiced as for other respiratory and enteric viruses to prevent a nosocomial spread [11]. Patients who undergo T cell replete related or unrelated match transplants, haploidentical transplant and patients with GVHD are at a higher risk of adenovirus infection or reactivation [12, 156, 157]. In these high-risk patients weekly monitoring of adenovirus viral load is recommended [11]. Tapering immunosuppression facilitates in treating adenoviral infections [12]. A reduction with viral load has been shown with ribavirin in some case reports. However, larger case series did not show reduction in viral load or clinical effect with ribavirin usage [158, 159]. Preliminary clinical data citing reduction in adenoviral disease and infection using ribavirin prophylaxis have been reported but further studies are needed [160]. Cidofovir has shown to be effective in pre-emptive treatment and premedication with probenecid and hyperhydration is recommended to prevent nephrotoxicity [161]. Brincidofovir has been successfully used in immunocompromised patients who had failed cidofovir [162]. Currently it is available on compassionate grounds for resistant adenovirus infections [163].

3.9 Polyomavirus

BK virus and JC virus are the two polyomaviruses of major importance. Urinary shedding of BK virus occurs in 60 to 80% of HSCT patients but less than 1/5th of the patients develop BK virus-associated hemorrhagic cystitis. Major disease manifestations include BK virus-associated hemorrhagic cystitis which typically occurs after engraftment [164]. This should be differentiated by bladder toxicity caused by urotoxic conditioning regimens. The diagnosis is made by the presence of hematuria and high urine BK viral load [165]. There are sporadic cases of BK virus-associated nephropathy, JC virus-associated hemorrhagic cystitis and multifocal leukoencephalopathy [166]. There is no evidence to support infection control measures in a patient with BK viruria [11]. Reduction in immunosuppression is effective in the treatment of BK virus infection [167]. Hyperhydration provides effective prophylaxis. Specific antiviral prophylaxis is not available. Levofloxacin prophylaxis has been tried in renal transplant patients. This failed to achieve reduction in BK viruria and viremia and also lead to antibiotic resistance and tendinitis [168]. A recent meta-analysis also concluded that fluoroquinolone prophylaxis fails to reduce incidence of BK viremia in renal transplant recipients [169]. Treatment of hemorrhagic cystitis using leflunomide has been reported in 2 retrospective studies showing an overall complete response of 63% [170, 171]. Treatment of hemorrhagic cystitis using Cidofovir has been tried. However, due to the toxicity of the drug and lack of randomized controlled studies, it is controversial [165]. Given the limited efficacy of pharmacologic treatments, results of adoptive immunotherapy using BK virus specific cytotoxic T lymphocytes (BKV-CTLs) are encouraging. A

preliminary analysis of 9 HSCT patients by Olson et al who received closely HLA – matched 3rd party BKV specific –CTLs showed 100% response. There were no infusion reactions. All patients achieved response by day 14 of infusion. 2 of 5 patients with partial response required 2nd CTL infusion from a different donor. The response in all cases was sustained. One patient developed grade 2 duodenal GVHD which was treated with systemic steroids [172].

4. Conclusions

Viral infections pose a clinical challenge in post HSCT patients leading to increased mortality and morbidity. Prompt recognition of symptoms and reproducible antiviral assays are essential in initiating therapy. Centre specific guidelines regarding prophylaxis, monitoring and pre-emptive therapy based on the resources available are required to successfully prevent and manage viral infections.

Author Contributions

SK Helped in drafting the manuscript; SW helped with bibliographic search; AS helped with bibliographic search; HG helped with revision of the manuscript; ME helped with the concept, revision and finalization of the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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