Chapter 29

Viral Infections in Hematopoietic Stem Cell Transplant Recipients

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1. Introduction

Viral infections are important as causes of morbidity and mortality after allogeneic stem cell transplantation (SCT). Severe viral infections are more common after unrelated and mismatched donor SCT and in particular after haploidentical SCT. B-cell function and specific antibodies are the main defense mechanisms against infection with exogenous viruses, thus reducing the risk for reinfection in already seropositive individuals. On the other hand, T-cell function in particular cytotoxic T-cell function is the main mechanism for preventing severe viral disease and also for the control of viruses such as herpesviruses that can cause latency and thus reactivate in an immunocompromised individual. The immune defects in SCT-patients are frequently complex with defects in cytotoxic T-lymphocyte, helper T-lymphocyte, NK-cell, and B-lymphocyte functions. T-cell dysfunction is usually most important early after SCT while deficient B-cell reconstitution can remain for many years after SCT. Furthermore, since loss of specific antibodies occurs frequently over time after allogeneic SCT, this will also increase the risk for reinfections with previously encountered viruses such as measles or varicella-zoster virus (VZV) and allow reactivation of viruses controlled by antibodies such as hepatitis B virus (HBV) [1, 2].

2. Diagnosis of Viral Infections

Many different techniques have been developed for diagnosis of viral infections. A summary is shown in Table 29-1. During recent years, important advances have been made through the use of rapid nucleic acid testing improving sensitivity and thereby making specific diagnosis and monitoring of viral infections feasible. The most commonly used technique is polymerase chain reaction (PCR) especially when used for determining viral load. Other techniques such as the hybrid capture assay, NASBA or branched-DNA have been applied and have shown good sensitivity and high specificity. The source of

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Table 29-1. Main use of diagnostic tests for virus infections in stem cell transplant recipients.

Virus	Serology	Histopathology/ immune histochemistry/DNA hybridization	IF	(q) PCR	Cell culture
HSV	Baseline risk stratification	Diagnosis of disease	Diagnosis of acute infection	Diagnosis of disease especially in CNS	Diagnosis of acute infection
VZV	Baseline risk stratification	Diagnosis of disease	Diagnosis of acute infection	Diagnosis of disease especially in CNS	Diagnosis of acute infection
CMV	Baseline risk stratification	Diagnosis of disease	Monitoring (antigenemia)	Monitoring (blood); diagnosis of CNS disease. Other applications need further studies	Diagnosis of disease
EBV	Baseline risk stratification	Diagnosis of disease	Rarely useful	Monitoring (blood)	Rarely useful
HHV-6	Not useful	Diagnosis of disease	Rarely useful	Diagnosis of CNS disease	Rarely useful
Respiratory viruses	Not useful	Diagnosis of disease	Diagnosis of infection	Diagnosis of infection	Diagnosis of acute infection
Adenovirus	Not useful	Diagnosis of disease	Diagnosis of infection	Monitoring (blood); diagnosis of CNS disease	Diagnosis of acute infection; typing
BK-virus/JC-virus	Not useful	Sometimes useful	Not applicable	Diagnosis of infection (urine, blood); diagnosis of CNS disease	Rarely useful

EM electron microscopy; *IF* direct immunofluorescence; *q* quantitative; *PCR* polymerase chain reaction

the specimen, the timing of collection in relation to onset of symptoms, the rapidity and method of delivery to the laboratory, and the clinical and epidemiological data provided to the laboratory are important factors that directly affect the likelihood of successful isolation and/or identification of a viral pathogen.

3. Cytomegalovirus

3.1. Risk Factors

Cytomegalovirus (CMV) remains one of the most important complications to allogeneic bone marrow and stem cell transplantation. CMV can cause multi-organ disease after SCT including pneumonia, hepatitis, gastroenteritis, retinitis, and encephalitis. CMV disease can occur both early and late after transplantation [3–6]. Seropositivity of the patients remains a risk factor for transplant related mortality in unrelated transplant patients despite major advances in early diagnosis and management [7–9] Seronegative patients with seropositive stem cell donors develop primary CMV infection in about 30% and have an increased mortality in bacterial and fungal infections [10]. In a study using the EBMT registry database, CMV seropositive patients receiving seropositive unrelated donor grafts had improved survival and reduced TRM compared to those receiving seronegative grafts and a similar result was found in a single center study [11, 12]. The mechanism for this positive effect was hypothesized to be the transfer of CMV-specific donor cells with the grafts. Other studies have, however, failed to find this correlation and therefore, it remains controversial [13]. Other identified risk factors include acute and chronic GVHD and the use of mismatched or unrelated donors. Sirolimus as prophylaxis against acute GVHD has been reported to result in a lower risk for CMV reactivation [14]. The mechanism behind this reduced risk is unknown. CMV might also be one factor in the pathogenesis of chronic GVHD [15, 16].

3.2. Prophylaxis Against CMV Infection and Disease

Since the prognosis of established CMV disease is still poor, preventive measures are very important. The available strategies can be divided into prevention of a primary infection, recurrence of CMV (prophylaxis), and prevention of development of disease when a reactivation has occurred (preemptive therapy). Serology should be performed before SCT in both patients and donors. Patients who are CMV seronegative before SCT should if possible be transplanted from a CMV seronegative donor [17]. To reduce the risk of CMV transmission from blood products, blood products from CMV seronegative donors or leukocyte depleted blood products should be used, as CMV is mainly harbored in the leukocyte fraction [18–20]. Which strategy is preferable is still not definitively settled [21, 22]. In many centers, and even in entire countries, leukocyte filtration is obligatory for all blood products and no study has in a controlled fashion compared the benefit of use of seronegative blood to that of already filtered blood products. IV immune globulin has at best a minor effect and has therefore been replaced by other more effective strategies. High doses of acyclovir and valacyclovir can reduce the risk for CMV

infection [23–26]. Valacyclovir can reduce the need for preemptive therapy to approximately 50% [26]. I.v. ganciclovir is effective for prevention of CMV disease [27, 28]. However, these studies were performed before the widespread use of growth factors such as G-CSF and ganciclovir induced neutropenia was a problem in both studies. Valganciclovir is the product of ganciclovir giving similar blood levels as i.v ganciclovir but no study has evaluated its efficacy as a prophylactic agent.

3.3. Preemptive Therapy

Preemptive therapy based on early detection of CMV has become the most commonly used strategy for prevention of CMV disease after allogeneic SCT [29, 30]. As early identification of patients at risk for developing viral disease reduces virus-related morbidity and mortality, monitoring with sensitive techniques such as antigenemia or quantitative PCR is indicated in all allogeneic SCT patients. Viral load monitoring seems to be of importance for assessing the risk for CMV disease or the efficacy of antiviral therapy [31–35].

Ganciclovir is the most used drug for preemptive therapy. Valganciclovir has been studied in several uncontrolled studies and in a small randomized pharmacokinetic study and gives higher drug exposure compared to i.v. ganciclovir and similar efficacy [36]. Both drugs are associated with bone marrow suppression and renal toxicity. Antiviral resistance can develop on the basis of mutations in the CMV genes, which the drugs inhibit. However, virus mediated antiviral resistance is quite rare in SCT patients while “clinical” resistance based on rapid replicating virus in the severely immunocompromised patients is quite common especially early after initiation of antiviral therapy. Increasing antigenemia or CMV DNA is therefore commonly not a sign of antiviral resistance and does not necessitate change of therapy [32, 37].

Although foscarnet is as effective as ganciclovir [38], it is more commonly used today as a second line drug. Foscarnet is associated with renal toxicity and electrolyte disturbances. The duration of preemptive therapy has varied in the published studies. One strategy is to continue therapy until day 100 after SCT [39] while the other possibility is to treat until the indicator test becomes negative, usually resulting in a shorter duration of therapy [38, 40]. Also the combination of ganciclovir and foscarnet has been used [41, 42]. Cidofovir (3–5 mg/kg per week) has also been used as a second-line agent but is associated with renal toxicity [43–45]. Case reports have been published of treatment with leflunomide or artesunate in patients failing other antiviral therapies [46–48].

3.4. CMV Disease

Appropriate diagnostic procedures should be undertaken in patients suspected to have CMV end-organ disease [49]. The prognosis in patients with established CMV disease is still poor [3, 50]. Standard therapy of CMV pneumonia has been intravenous ganciclovir combined with high dose immune globulin but this standard was questioned by the results of an uncontrolled study suggesting that the advantage of adding immune globulin is limited with no improvement in survival over ganciclovir therapy given alone [50]. For patients with CMV disease other than pneumonia, the addition of immune

globulin does not seem to be beneficial [51]. A retrospective survey reported that cidofovir could salvage nine of 16 patients with CMV pneumonia failing therapy with ganciclovir, foscarnet, or the combination [43].

3.5. Immune Monitoring and Immune Therapy

The lack of specific immunity to CMV, both regarding cytotoxic T-cell (CTL) response and helper T-cell response to CMV, has been associated with a high risk for CMV disease [3, 5, 52, 53]. Monitoring of CD8 and/or CD4 CMV specific T-cells has therefore been studied and different techniques can be applied including detection by tetramers containing immunodominant peptides from CMV or measurement of peptide-specific intracellular cytokine staining [54–59]. Riddell et al. have shown that specific CTL can be cloned in vitro, safely be given to the patient, and their activity be detectable during follow-up [52, 60, 61]. Techniques for isolation of CTL including the use of peptide pulsed dendritic cells, selection by tetramer technology, or vaccination with peptide pulsed dendritic cells have been developed and several centers are testing these strategies in clinical trials [58, 62–66].

4. Herpes Simplex Virus

Herpes simplex virus (HSV) can cause local and rarely disseminated infections after SCT. Serology is useful for determining the risk for reactivated HSV infection and should be performed before transplantation. The manifestations in transplant patients can be atypical causing generalized inflammation and pain from the mucous membranes without classical vesicular or ulcerative lesions. Generalized and invasive disease can occur but encephalitis is not more frequent in immunocompromised compared to immune competent patients. Acyclovir prophylaxis is indicated in all HSV seropositive SCT recipients [67]. The duration of antiviral prophylaxis should be at least during the aplastic phase but a longer duration should be considered in patients with GVHD or a history of frequent reactivations before the transplantation [67]. A recent study has shown a 2-year probability for HSV disease of 32% when acyclovir was given for 30 days compared to 0% if prolonged prophylaxis was given [68]. Acyclovir resistant virus strains are still quite rare but seem to be more common in high risk patients such as unrelated donor transplants or patients with severe GVHD [69–71]. However, the risk was reported to be very low in patients receiving prolonged prophylaxis [68]. The recommended drug for acyclovir-resistant HSV is foscarnet [72–74]. Two reports have described mutants resistant to both acyclovir and foscarnet [69, 70]. Currently, the only available antiviral drug available for treatment of double resistant HSV is cidofovir.

5. Varicella-Zoster Virus

A primary VZV infection (varicella) is an uncommon but severe complication in SCT patients [75]. Seronegative patients are at risk for developing varicella and preventive measures are therefore indicated. The risk is highest in children but cases of varicella-like disease in seropositive adults becoming seronegative

after SCT have been described. Serology is therefore important to identify patients at risk for varicella and should be performed in all patients before and at regular intervals after SCT. Varicella-zoster immune globulin is the recommended prophylactic measure in seronegative patients if it can be given within 4 days after a household or other type of close exposure [67]. Another option is prophylaxis with acyclovir or valacyclovir but there are no published data regarding effectiveness. Reactivated VZV infection – herpes zoster – develops in approximately one third of the SCT recipients in the absence of prophylaxis [78–79]. Severe and fatal cases have also been reported after allogeneic SCT with reduced conditioning. Herpes zoster is usually dermatomal but disseminated and potentially fatal infections with visceral involvement can occur [75]. The clinical picture might be atypical with gastro-intestinal, liver, or CNS disease occurring in the absence of skin lesions. The risk of herpes zoster is highest between 3 and 6 months after transplantation and decreases thereafter steadily over the first 2 years after SCT [80]. Therefore, the duration of antiviral prophylaxis must be long to be effective. A rebound phenomenon occurs when prophylaxis is given for 6 months [81, 82] but does not exist if prophylaxis is given for 12 months [83]. Longer prophylaxis reduces the rates even further especially in patients with chronic GVHD [80]. The recommended therapy for primary varicella, disseminated herpes zoster, or localized zoster developing early after SCT or in patient on treatment for GVHD is intravenous acyclovir 10 mg/kg (or 500 mg/m^2) three times daily. For localized dermatomal herpes zoster occurring late after SCT especially on patients of immunosuppression, clinical experience suggests that oral therapy with acyclovir, famciclovir, or valaciclovir is effective in the majority of patients [84, 85].

6. Epstein-Barr Virus

Epstein-Barr **V**irus (EBV) is frequently detected after allogeneic SCT [86–90]. However, only a few case reports have suggested that it directly causes significant disease such as meningo-encephalitis [91]. EBV induced post-transplant lymphoproliferative disease (PTLD) is a serious complication to allogeneic SCT. Although the incidence of EBV-PTLD is generally lower than 2% following allogeneic SCT, it may increase up to 20% in patients with risk factors such as mismatched donor SCT, the use of an EBV positive donor to an EBV negative recipient, T-cell depletion, ATG therapy, and other forms of intensified immunosuppression for prevention and treatment of GVHD [92, 93]. Cord-blood SCT recipients receiving reduced intensity conditioning including ATG were reported to have a high risk for EBV associated complications [94]. EBV-PTLD usually occurs during the first 3 months after SCT although it can present later.

PTLD usually presents during the first months after SCT as a polymorphic polyclonal lymphoproliferation that may result in monoclonal malignant lymphoma if left untreated. EBV DNA load monitoring in peripheral blood has been studied as a predictor for EBV-PTLD but the variations in the “in house” developed assays and the use of different sample types such as whole blood, serum/plasma, or PBL make it difficult to draw firm conclusions [88, 95–97]. The usefulness of viral load monitoring depends on the likelihood for a patient developing PTLD. The positive predictive values vary greatly between different studies [98] with the highest for patients having risk factors for EBV-PTLD

[95, 96, 98]. Despite these uncertainties, monitoring of viral load seems to be a valuable tool especially in high risk patients. As many different techniques using different materials and primers exist, no cut-off viral load for initiating therapy can be recommended. However, rapid increase in viral load has been suggested to be associated with a high risk for EBV-PTLD.

The first management option in a patient at high risk for PTLD is, if possible, to reduce the immunosuppression. Antiviral therapy might lower the EBV viral load but whether this influences the risk for PTLD is doubtful. Rituximab has been used as "preemptive therapy" in several patient series with good results but no controlled data exist [88, 94, 98, 99]. Another prophylactic option is to give infusions with EBV specific CTL [100–102]. There is no established therapy for treatment of PTLD. Rituximab has been used after both solid organ and SCT [90, 103–106]. Cloned EBV specific donor T-cells [100, 102], partially HLA-matched allogeneic donor CTL [107], and unspecific donor lymphocyte infusions have also been used as treatment of PTLD [108].

7. Human Herpes Virus Type 6

Human Herpes Virus Type 6 (HHV-6) exists in two subtypes (A and B) that differ from each other in 4–8% of the DNA. Subtype B is the cause of exanthema subitum in childhood. HHV-6 infection is very common early in life; hence the rate of seropositivity in older children and adults is more than 95%. Serology is therefore not helpful in patient management. There is no "gold standard" diagnostic test for HHV-6 infection but quantitative PCR has been used to better define of the contribution of HHV-6 to post transplant complications [109–111]. A possible confounding factor is that the HHV-6 genome can be integrated into cellular DNA resulting in high levels of HHV-6 DNA in blood samples including PBL [112, 113]. The best documented clinical manifestations of HHV-6 are encephalitis and bone marrow suppression.

HHV-6 has a propensity for the CNS and although HHV-6 DNA can occasionally be detected in the CSF of asymptomatic SCT recipients [114, 115], the combination of symptoms of encephalitis with detection of HHV-6 DNA is suggestive of HHV-6 disease of the CNS. Approximately 35 case reports have been published [110, 114–128]. A summary of published information around these cases regarding patient characteristics, diagnostic findings, and outcome of HHV-6 CNS disease in SCT patients is shown in Table 29-2. Lethargy, confusion, convulsions, and decreased consciousness are the predominant clinical manifestations of HHV-6 encephalitis. Focal neurological findings have been reported but are less common. Magnetic resonance imaging can show abnormalities but it can also be normal. These changes included multiple, non-enhancing, low attenuation lesions in the gray matter. EEG usually shows diffuse changes. The prognosis is poor unless the encephalitis is treated with antiviral drugs. Both ganciclovir and foscarnet have been reported being effective against HHV-6 meningo-encephalitis after SCT (Table 29.2) [114, 129]. Another possible manifestation of HHV-6 is bone marrow suppression or delayed engraftment as HHV-6 can infect hematological progenitor cells and reduce colony formation [87, 110, 130–132].

Table 29-2. Patient characteristics, diagnostic findings, therapy, and outcome of SCT patients with suspected or proven HHV-6 encephalitis.

Patient characteristics	***N*=37**
Median age	41 (12–66)
Unrelated or mismatched	26
Sibling donor	6
Autologous	1
Acute GVHD grade II–IV	16/25
CSF findings	
Pleocytosis	15/32
Increased protein	21/32
HHV-6 DNA	35/35
Radiographic findings	
MRI changes	22/34
CT changes	4/17
EEG changes	22/22
Survival of patients receiving therapy	17/28
Ganciclovir/valganciclovir	5/7
Foscarnet	13/15
Acyclovir	1/2
Foscarnet + ganciclovir given in combination or consecutively	3/10

8. Respiratory Viruses

Respiratory viruses including respiratory syncytial virus (RSV), parainfluenza viruses, coronaviruses, rhinoviruses, and influenza A and B are widespread in the community with major seasonal variations. Recently several new viruses have been discovered including bocavirus and two papovaviruses that can cause respiratory disease. The epidemiological situation in the local community has been shown to influence the risk for infection in the SCT patients. This at least partly explains the variation in frequencies of diagnosed infections between different studies [133–136]. Respiratory viruses can be spread nosocomially through immune competent staff and patient relatives and outbreaks of both RSV and parainfluenza infections have been documented in transplant units [137–141]. Thus, infection control measures including isolation of symptomatic patients, use of sensitive diagnostic procedures, and as far as possible avoidance of exposure to infected persons including family and staff are important in the management of respiratory infections. The influence of respiratory virus infections on transplant related mortality has been estimated by a study

by the EBMT. In that study 1.1% of allogeneic patients transplanted at the participating centers died of a respiratory virus infection [133]. Furthermore, RSV [142, 143] and parainfluenza infections [143] have also been implicated in the development of late respiratory dysfunction after SCT.

9. Respiratory Syncytial Virus

RSV has been the cause of outbreaks in SCT patients forcing closure of transplant units [136, 144–146]. In a prospective survey, the overall mortality in patients with a RSV lower respiratory tract infection was 30% and the RSV associated mortality 17% [133]. More recently, the impact of RSV seems to have been reduced [134, 147] possibly as a result of identification of patients with lesser degree of symptoms. Several studies have analyzed risk factors for progression to lower respiratory tract disease. The outcome is worse after allogeneic and in patients with lymphopenia [133, 148]. Patients having documented RSV infection pretransplant should have their allogeneic transplant postponed if possible [149], while this does not seem to be as important for patients undergoing autologous SCT for myeloma [150].

There is no established therapy for RSV. In a small randomized trial there was no difference between patients receiving ribavirin or no therapy regarding the risk for progression to pneumonia, but there was a tendency for a greater viral load decrease in ribavirin treated patients ($p=0.07$) [151]. In an uncontrolled study, 4 of 14 patients treated with the combination of ribavirin and high dose iv immune globulin developed pneumonia [152]. In the prospective EBMT survey, no regimen was superior to any other [133]. In a small phase I study of the RSV monoclonal antibody palivizumab, three patients were treated for an upper respiratory tract infection and none developed lower respiratory tract disease [153]. Only uncontrolled phase II treatment studies of RSV pneumonia have been reported. There are no proven benefits with any drug or combination, but patients treated when ventilator dependent usually have dismal outcome [136]. Ljungman et al reported similar outcomes with ribavirin given intravenously and as aerosol [133]. On the other hand, McCarthy et al. reported 26 patients with RSV infections and no apparent effect on outcome with ribavirin therapy [154]. DeVincenzo et al. reported that 10/11 children treated with a high-titer anti-RSV immune globulin in combination with ribavirin survived [155]. In a series of 16 patients with RSV pneumonia treated with ribavirin aerosol and/or RSV Ig, 14 survived [147]. Despite the lack of controlled data, many centers use ribavirin to treat RSV infections especially in allogeneic SCT recipients.

9.1. Parainfluenza Viruses

Parainfluenza viruses can give severe and fatal infections after SCT. The subtype most associated with severe infections is type 3 [141, 156–158]. In a retrospective study, unrelated donor transplant was the only identified risk factor for parainfluenza infection [141] and parainfluenza infection was an independent predictor of mortality [141]. The usefulness of antiviral therapy is doubtful. Wendt et al and Nichols et al both failed to find any effect of ribavirin therapy [141, 158]. Other studies have shown some indications of effectiveness by ribavirin therapy [142, 157, 159].

10. Influenza Viruses

Influenza is an important problem to consider in SCT recipients. The mortality has been reported to be around 15% in untreated patients [133, 160]. The mortality is highest in patients developing pneumonia [161]. Fatal influenza infections can occur several years after an allogeneic SCT in particular in patients with chronic GVHD [133].

The primary mode for prevention of influenza is vaccination and should be given to all transplant patients from 4 months after transplantation and yearly while the patients are immunosuppressed [67, 162]. The antibody responses have been poor when vaccinations are performed early after SCT [163, 164] but clinical protection might still be achieved [165]. Vaccination of family members and hospital staff to reduce the risk for transmission of influenza is recommended [133]. The possibilities for prevention with antiviral agents include today mainly the neuramidase inhibitors (zanamivir and oseltamivir). No controlled study has been performed in SCT patients, but in an uncontrolled study oseltamivir was given to 41 patients with influenza of whom two developed pneumonia and none died [166]). In another series 6 of 34 untreated patients, one of eight treated with rimantadine, and none of nine patients treated with oseltamivir developed pneumonia [161]. One concern is the reported rapid development of oseltamivir resistant influenza viruses.

11. Other Respiratory Viruses

Metapneumovirus is a paramyxovirus causing upper and lower respiratory tract infections in children. Martino et al found in a prospective study an incidence of 5% in allogeneic and 3% in autologous SCT recipients [135]. Forty-four percent of the patients with metapneumovirus infections in allogeneic SCT recipients developed pneumonia. Fatal infections have been reported [167]. The impact of other respiratory viruses including rhinoviruses, coronaviruses, and the recently discovered boca- and respiratory papovaviruses needs further study. No therapy exists for any of these recently discovered respiratory viruses.

12. Adenoviruses

Adenoviruses cause a number of clinical syndromes in immune competent individuals that are usually mild and self-limiting, but more severe manifestations have also been reported. Although 51 distinct adenovirus serotypes have been identified, most human diseases are associated with only one-third of these types. Adenovirus infections can result in morbidity and mortality after allogeneic SCT. The frequencies of adenovirus infections vary between studies. Overall, there is a higher frequency in children. Flomenberg et al. reported a frequency of 31% in children compared to 14% in adults [168]. In a study using PCR monitoring of pediatric SCT recipients, Lion et al. reported that 27% of the patients had adenovirus DNA detected [169] while Hoffman et al. in a study of pediatric SCT recipients detected adenovirus in 47% of the patients [170]. Other reports give frequencies of 3–29% [171–176]. The factors influencing the detection frequency seem to be the age of the population studied, whether

the study was prospective or retrospective, and the diagnostic technique used, but there also seems to be a center effect with some centers experiencing a major adenovirus problem while it is rather rare in other centers.

The most serious disease manifestations are pneumonia, encephalitis, and fulminant hepatitis. However, hemorrhagic cystitis and gastroenteritis seem to be more common. The most commonly recognized risk factors for adenovirus disease in allogeneic SCT recipients are younger age, T-cell depletion, GVHD, the use of mismatched and unrelated donors, the use of unrelated cord blood grafts, and adenovirus detected from more than one site [168, 170–174, 177, 178]. Identification of adenovirus in peripheral blood has also been associated with an increased risk for adenovirus disease [169].

There is no established either prophylaxis or therapy for adenovirus infections in SCT recipients. Ribavirin has been used in case reports with varying outcome [173, 179–185]. Morfin et al. reported that the in vitro efficacy varied among different subgenera of adenovirus with group C isolates being more sensitive in vitro to ribavirin compared to other subgenera [186]. This might explain some of the inconsistencies in the treatment results with ribavirin. Cidofovir might have effect against adenovirus infections but no controlled studies have been performed in SCT recipients. Reported results have been varying but it seems probable that cidofovir has an anti-adenoviral effect in many patients but it alone cannot give long-term control as development of a specific T-cell response is necessary [187–193]. Similar to CMV and EBV, CTL based immunotherapy is under development for adenovirus [194, 195].

13. Hepatitis B and C Viruses

In patients who are HBsAg positive before transplantation there does not seem to be an obvious increased risk for severe liver complications after transplantation [196, 197] and long-term survival is similar in HBV-positive and negative patients [198]. Patients who are anti-HBs positive at the time of transplant can during long-term follow-up become HBsAg and HBV-DNA positive and also develop a flare of acute hepatitis because of loss of specific antibodies to HBV [2, 199–202]. In a seronegative recipient, the use of an HBV antigen positive marrow donor should if possible be avoided as the risk for transfer of HBV is high and hepatitis is likely to develop [203]. If a seropositive donor must be used, vaccination of the patient before transplant would be logical as patients who are antibody positive to HBV before transplant are less likely to develop severe liver complications [196, 204]. HBV specific immune globulin can be given to the patient before transplantation [196]. Lamivudine has been used in SCT patients to prevent reactivation [205–211].

Patients with hepatitis C virus (HCV) and abnormal liver function tests were reported having an increased risk for hepatic VOD [212, 213]. If the stem cell donor is HCV RNA positive the risk for transmission to the patient is very high [214]. Therefore, the use of an HCV positive donor should be avoided if alternatives exist. HCV-infected long-term survivors of allogeneic SCT have a high risk for development of liver cirrhosis [215, 216]. Therapy with interferon together with ribavirin using similar dose and duration as in non-transplant individuals seems to be safe and effective although no controlled study exists [217–219].

14. Papovaviruses

Papovaviruses are a group of DNA-viruses with two members – JC-virus and BK-virus – that can be pathogenic in SCT patients. JC-virus is the agent causing progressive multifocal leukoencephalopathy (PML) and BK-virus has been implicated in hemorrhagic cystitis and nephropathy in transplant recipients. Both BK- and JC-viruses are excreted in the urine of many patients after transplant. Papovaviruria has been associated with hemorrhagic cystitis although there is no absolute correlation. Higher viral loads in urine, mutations in a viral gene, and BK-viremia have been correlated to hemorrhagic cystitis [220–226]. However, also transplant factors such as allogeneic rather than autologous SCT, myeloablative conditioning, and the use of mismatched or unrelated donors have also been shown to correlate to hemorrhagic cystitis [223, 224, 227, 228]. Thus, the pathogenesis of hemorrhagic cystitis seems to be multifactorial [229]. Cidofovir has in small uncontrolled studies been reported to be effective against polyoma virus-associated HC [230, 231]. There is no established therapy for PML although cidofovir and ara-C have been given with varying results.

15. Other Viruses

Measles can be fatal in immunocompromised hosts [232, 233] and severe cases have been reported in SCT recipients [234, 235]. Most patients will lose immunity during extended follow up and are therefore vulnerable to infection [236]. Vaccination against measles has been shown to be safe in patients without GVHD or ongoing immunosuppression. The seroconversion rates varied between 54 and 100% [1, 237, 238].

Parvovirus B19 exhibits a marked tropism for human bone marrow and replicates only in erythroid cells. Occasional case reports of protracted parvovirus infections have been published after stem cell transplantation [239, 240].

Rotavirus infections mostly affect otherwise normal children below 3 years of age. Reinfection in adults can occur. The symptoms are usually diarrhea and vomiting. In BMT recipients, gastroenteritis caused by rotavirus has been described [241]. Electron microscopy and ELISA can confirm the diagnosis. There is no proven effective treatment, although two cases described by Kanfer et al. [242] appeared to respond to oral immunoglobulin (6 g daily for 5 days). Coxsackie A1 virus infection with diarrhea and a significant mortality has been reported in BMT patients [241]. The diagnosis can be obtained with virus isolation from stool, cerebrospinal fluid, secretions from nose and pharynx, tears, and urine and by serology. Prolonged enteroviral infection has been described in a BMT recipient who developed pericarditis and heart failure posttransplant [243]. Although no formal study has been performed, it seems likely that these outbreaks are associated with the epidemiological situation in the community and awareness of the local situation can be of value.

West Nile virus can be transmitted by blood products or from the stem cell donor and has been associated with severe diseases including fatal outcome after SCT [244–248].

16. Summary

Viral infections remain important challenges for the physician taking care of SCT patients. This includes "old" pathogens that might change the clinical presentations when new techniques are included in the treatment of SCT patients for example the use of haploidentical donors, cord blood grafts, or new immunosuppressive agents. New viral pathogens might also be introduced into the SCT patient population. On the other hand new management options need to be carefully evaluated both regarding new diagnostic options and antiviral agents.

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