Challenges and options in the management of viral infections after stem cell transplantation

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Abstract During the period of profound combined immunodeficiency after bone marrow or peripheral blood stem cell transplantation (SCT), patients are at increased risk for serious viral disease. Recent advances in rapid diagnostic methods and the introduction of potent antiviral compounds have made it possible to establish efficient management strategies for several herpesviruses. Acyclovir, valaciclovir, and famciclovir are widely used for the treatment of herpes simplex virus or varicella zoster virus disease. Intravenous ganciclovir, foscarnet, and cidofovir are available for prevention or therapy of cytomegalovirus disease, and oral valganciclovir could become a valuable alternative to intravenous treatment if shown to be effective and safe after SCT. Preliminary data on pleconaril for therapy of picornavius disease are promising. Future investigations may help to clarify the role of the neuraminidase inhibitors zanamivir and oseltamivir in the management of influenza in SCT recipients. The emergence of viruses resistant to antiviral drugs is of concern, and alternative treatment strategies need to be defined.

Keywords Stem cell transplantation - Virus infection - Antiviral prophylaxis - Antiviral therapy - Antiviral drug resistance

Introduction

After bone marrow or peripheral blood stem cell transplantation (SCT), patients are at elevated risk for severe viral disease, particularly during the period of combined immunodeficiency early after transplantation [9, 14, 20, 21, 27, 42, 62, 65, 78, 79, 80]. DNA viruses are generally a more frequent cause of infection than RNA viruses, which is related to their propensity to establish long-term latency after primary infection and to reactivate during subsequent periods of immunosuppression [13, 41, 62, 65, 70, 74].

In recent years, major advances have been made in the management of diseases due to several herpesviruses, including herpes simplex virus (HSV), varicella zoster virus (VZV), and cytomegalovirus (CMV), and promising treatment approaches are emerging for picornavius disease and influenz. Progress was made possible primarily by the introduction of efficient antiviral drugs into clinical practice. Table 1 lists 16 compounds that are presently available or will shortly be approved for the treatment of various viral infections. An additional factor contributing to progress was the development of rapid and sensitive diagnostic methods, such as the shell-vial culture, antigen detection assays, and the polymerase chain reaction (PCR), which permit the detection of viral infections at an early stage [18, 25, 29, 44, 45, 46, 48, 51, 52, 82]. Results obtained with these techniques enable clinicians to make timely therapeutic decisions.

Rapid diagnostic tests have also facilitated the introduction of the preemptive treatment strategy, which consists in initiating antiviral drug therapy only when a viral infection is documented, to prevent the occurrence of viral disease [18, 23, 66]. In contrast to antiviral drug prophylaxis, the preemptive treatment approach restricts antiviral treatment to patients at the highest risk for viral...
Table 1 Antiviral drugs that are currently licensed or will be approved shortly, and their main treatment indications. Drugs used exclusively for treatment of human immunodeficiency virus infection are not listed

<table>
<thead>
<tr>
<th>Antiviral drug (prodrug)</th>
<th>Main treatment indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir (valaciclovir), penciclovir (famciclovir)</td>
<td>Herpes simplex virus, varicella-zoster virus</td>
</tr>
<tr>
<td>Ganciclovir (valganciclovir), cidofovir, fosarnet, fomiviren</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Respiratory syncytial virus</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Hepatitis B</td>
</tr>
<tr>
<td>Pleconaril</td>
<td>Picornaviruses</td>
</tr>
<tr>
<td>Amantadine, rimantadine*</td>
<td>Influenza A</td>
</tr>
<tr>
<td>Zanamivir, oseltamivir</td>
<td>Influenza A and B</td>
</tr>
</tbody>
</table>

* Not licensed in Europe

disease, which is particularly important in view of the toxicity and costs associated with some of the antiviral compounds currently available.

Human herpesviruses

Herpesviruses are among the most common causes of viral disease after allogeneic and autologous SCT [57, 59]. So far eight viruses have been identified that belong to the human herpesvirus family. Treatment strategies have been established for infections with HSV types 1 and 2, VZV, and CMV. A possible therapeutic effect of licensed antiviral drugs against Epstein-Barr virus and human herpesviruses 6, 7, and 8 in SCT recipients has not been investigated in controlled trials, and firm recommendations on the treatment of these viruses are therefore not possible [59, 70, 74].

Herpes simplex virus

Following SCT, HSV lesions develop mainly at mucocutaneous sites, but esophageal HSV disease is also frequent and is present in about 10% of patients with upper gastrointestinal symptoms [9]. HSV disease results from reactivation of latent virus in most cases, and antiviral drug prophylaxis is thus primarily aimed at HSV seropositive patients.

The antiviral drugs acyclovir, valaciclovir and famciclovir are licensed for treatment of HSV infection and disease (Table 1). Valaciclovir and famciclovir have an oral bioavailability 3–5 times that of oral acyclovir, which permits less frequent dosing and replacement of intravenous acyclovir for some indications, as discussed later [54, 72, 77].

Prophylactic intravenous or oral acyclovir has become a standard of care for HSV seropositive SCT recipients [9, 59]. The duration of prophylaxis is usually 3–5 weeks after the start of the conditioning regimen, but may be longer in allograft recipients who develop acute graft-versus-host disease. Oral valaciclovir and famciclovir have not been systematically studied for the prevention of HSV infection after SCT, but are probably as efficient as acyclovir. Intravenous acyclovir is the therapy of choice for severe mucocutaneous or visceral HSV disease in SCT recipients [59]. Oral acyclovir, valaciclovir, or famciclovir may be considered as therapeutic alternatives for less serious forms of HSV disease [3].

Varicella-zoster virus

Primary VZV infection causes chickenpox (varicella), and reactivation of VZV results in herpes zoster. Both manifestations of VZV infection require prompt treatment in SCT recipients to inhibit disease progression and prevent visceral dissemination. For therapy of chickenpox or zoster after SCT, the use of intravenous acyclovir for 7–10 days is the treatment of choice [59]. For moderately immune-deficient patients, high-dose oral acyclovir, oral valaciclovir, and famciclovir are possible treatment alternatives [3, 13]. A randomized comparison of famciclovir and oral acyclovir for therapy of localized zoster in immunocompromised hosts showed similar efficacy in terms of the time to cessation of new lesion formation, complete healing of lesions, or loss of acute pain, and the rates of zoster dissemination were no different between the two treatment groups [76].

Prevention of chickenpox in SCT recipients requires strict isolation from infectious individuals. Isolation procedures may be too late in some cases, however, because patients with chickenpox can be contagious up to 2 days before the onset of skin rash [73]. Following contact with an infected person, VZV-seronegative patients may benefit from infusions of VZV hyperimmune globulins if these are administered within 96 h of exposure [73]. Immunization with a VZV vaccine might become an additional option for the prevention of chickenpox and zoster in SCT recipients. In a noncomparative series of 15 children after SCT, the use of a live attenuated VZV vaccine was effective in preventing VZV disease for up to 2 years after immunization [69]. Among 75 VZV-seropositive SCT recipients randomized to receive a heat-inactivated VZV vaccine or no intervention, immunization was furthermore associated with better reconstitution of
specific cellular immunity and markedly less severe zoster [56].

VZV reactivation can occur for a long period after allogeneic SCT, but long-term antiviral drug prophylaxis is not advisable, since it only delays the development of zoster and carries the potential for induction of VZV resistance [26, 32, 49].

Cytomegalovirus

After SCT, patients are at increased risk of developing severe CMV disease following primary infection, re-infection, or reactivation of virus [57, 59]. In the absence of prophylactic measures, the incidence of CMV infection is 60–70% in SCT recipients when the graft donor or recipient is CMV seropositive, and one-third of allograft recipients and 10–20% of autograft recipients with documented CMV infection develop CMV pneumonia [20, 42, 61]. CMV pneumonia is a serious condition, which with the best presently available therapy is associated with a mortality rate of 45–78% [40, 59]. Because the outcome of CMV pneumonia remains serious despite antiviral therapy, major emphasis must be placed on the prevention of CMV disease in patients after SCT.

One strategy is the prophylactic use of antiviral drugs aimed at suppressing CMV reactivation and given to all patients irrespective of the results of virological monitoring [24, 43, 53, 81]. High-dose intravenous acyclovir prophylaxis mediates only partial protection from CMV disease in allograft recipients, and is ineffective in autograft recipients [7, 43]. Prophylactic intravenous ganciclovir in placebo-controlled studies of allograft recipients resulted in marked reduction of CMV disease, but was not associated with improved survival [24, 81].

An alternative approach to prevention of CMV disease is the preemptive drug treatment of CMV infection. Preemptive ganciclovir therapy based on positive CMV cultures was associated with both a significantly decreased incidence of CMV disease and better survival after allogeneic SCT compared to placebo [24]. However, 12% of patients screened for virus excretion in that trial, or 69% of those who developed CMV disease, had CMV disease diagnosed prior to or coincident with the first culture-based detection of CMV infection and thus did not benefit from preemptive antiviral treatment [24]. Newer diagnostic techniques, such as the CMV antigenemia assay or the PCR in peripheral blood specimens, permit the detection of CMV infection at an early stage while the systemic viral load is still low [18, 46]. A randomized comparison of PCR and viral cultures for initiation of preemptive ganciclovir therapy after allogeneic SCT showed that there were fewer cases of CMV disease and better survival in patients monitored by PCR [18]. In a multicenter randomized trial of foscarnet versus ganciclovir for preemptive treatment of CMV infection after allogeneic SCT, both antiviral drugs showed similar efficacy, but foscarnet was associated with significantly less hematotoxicity [66]. Preliminary results suggest that intravenous cidofovir might have a role as second-line preemptive therapy of CMV infection after SCT [40].

Valganciclovir, an oral prodrug of ganciclovir, was shown to have a bioavailability 10-fold that of oral ganciclovir in pharmacokinetic studies of CMV-seropositive human immunodeficiency virus (HIV)-infected patients and liver transplant recipients [8, 34, 50]. Systemic ganciclovir exposure achieved with oral valganciclovir is comparable to that yielded by intravenous ganciclovir [8, 50]. Thus, valganciclovir has the potential to replace intravenous ganciclovir in SCT recipients who are able to take oral medication if it is demonstrated to be safe and equally efficient [60].

Herpesvirus resistance to antiviral drugs

With the increasing use of antiviral drugs against herpesviruses, reports of herpesvirus resistance have emerged [58]. Infections due to drug-resistant HSV, VZV, and CMV have become a clinically important problem in HIV-infected patients and recipients of SCT or solid organ transplants [10, 11, 12, 16, 17, 19, 30, 31, 35, 37, 38, 63, 64, 71]. The incidence of HSV resistance to acyclovir after SCT has been reported to be between 7% and 14% [10, 11, 19]. While ganciclovir-resistant CMV infection develops in up to 27% of HIV-infected patients receiving long-term ganciclovir therapy, data on CMV resistance in SCT recipients are limited to a few cases, and the incidence of this complication remains undefined [17, 30, 63, 64, 71].

In the past, most patients with acyclovir-resistant HSV disease or ganciclovir-resistant CMV infection appeared to respond to foscarnet treatment [4, 63]. More recent studies indicate that strains of HSV or CMV may be multiresistant to antiviral drugs, and that foscarnet is not a valuable alternative in many cases of virus resistance [10, 11, 12, 17]. Future investigations should better define the incidence and clinical importance of herpesvirus resistance after SCT, and should establish alternative treatment strategies for drug-resistant viral disease.

Picornaviruses

The family of picornaviruses includes enteroviruses and rhinoviruses, which have a linear single-stranded RNA. Enteroviruses are divided into coxsackieviruses A and B, echoviruses, and polioviruses, and about 70 serotypes of enteroviruses have been identified. Following SCT, enterovirus infections may be disseminated and result in fatal outcomes [2, 5, 22]. In the past, treatment of enterovirus resistance to antiviral drugs.
Table 2 Pleconaril for treatment of enterovirus infections after stem cell transplantation. Data from [68]

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Dose (mg/day)</th>
<th>Virus detection</th>
<th>Clinical signs</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34 years</td>
<td>1200</td>
<td>Electron microscopy</td>
<td>Pleuro-pericardial effusions, rash</td>
<td>Improved</td>
</tr>
<tr>
<td>2</td>
<td>15 years</td>
<td>1200</td>
<td>Culture+</td>
<td>Encephalitis in remission</td>
<td>No relapse</td>
</tr>
<tr>
<td>3</td>
<td>13 years</td>
<td>600</td>
<td>Culture+</td>
<td>Neurological, diarrhea</td>
<td>Improved</td>
</tr>
<tr>
<td>4</td>
<td>15 months</td>
<td>15+</td>
<td>Culture+</td>
<td>Pneumonia</td>
<td>Improved</td>
</tr>
</tbody>
</table>

*mg/kg per day

* Died from pulmonary hemorrhage complicating acute myeloid leukemia

virus infection in immunocompromised hosts was largely supportive.

Pleconaril, a broad-spectrum antipicornaviral compound, has recently become available for clinical use [68]. Pleconaril acts by binding to a hydrophobic pocket in the viral capsid, thereby altering both receptor binding and viral uncoating [67]. The oral bioavailability of pleconaril makes it possible to achieve serum concentrations superior to those required to inhibit 90% of clinical enterovirus and rhinovirus isolates in vitro, and high concentrations of this agent are obtained in the central nervous system and nasal secretions [67]. Several phase III trials of pleconaril for various picornaviral infections have been completed or are ongoing [6].

A first report on the use of pleconaril in 38 patients with potentially life-threatening enterovirus infection yielded encouraging results [68]. In this study, adults received pleconaril at a dose of 200 mg or 400 mg three times a day, and children were treated with a dose of 5 mg/kg three times a day. The drug was given as an oral suspension for a total of 7–10 days. A favorable clinical outcome was observed in 78% of patients treated, and a virological response was noted in 92% of cases. Adverse events were minimal, and pleconaril was generally well tolerated. Four of the 38 patients treated with pleconaril were SCT recipients, and the characteristics and clinical outcomes of these 4 patients are summarized in Table 2 [68]. The promising results obtained in these patients justify further investigation of pleconaril in larger populations of SCT recipients who develop laboratory-confirmed enterovirus or rhinovirus disease.

Community respiratory viruses

Community respiratory viruses are an increasingly recognized cause of significant morbidity and mortality after SCT [27, 39, 78, 79, 80]. Of 217 adult SCT recipients hospitalized with acute respiratory disease during two consecutive winter seasons, 67 (31%) were infected by community respiratory viruses, and 49% of these infections were due to respiratory syncytial virus (RSV), 18% each to influenza viruses and to picornaviruses, 9% to parainfluenza viruses, and 6% to adenovirus [80]. In the absence of treatment, the case-fatality rate for lower respiratory tract infection and pneumonia was up to 100% for RSV, and was approximately one-third for parainfluenza and influenza viruses [27, 78, 79, 80].

Although rapid diagnostic methods are available for most community respiratory viruses, progress in the management of these infections is slow, which is in part related to the limited number of antiviral drugs against these viruses and in part to the lack of data from controlled intervention trials in immune-deficient hosts. For SCT recipients with established RSV pneumonia and respiratory failure, aerosolized ribavirin was generally ineffective, but it might be beneficial if given preemptively when only the upper respiratory tract is involved [27, 80]. Moreover, the combination of aerosolized ribavirin plus intravenous hyperimmune RSV globulins could yield better results in the treatment of RSV infection and deserves further study.

For treatment of influenza, amantadine, rimantadine, and the novel neuraminidase inhibitors, zanamivir and oseltamivir are presently available [1, 28, 47, 75]. The antiviral activity of amantadine and rimantadine is restricted to influenza A virus, and both drugs are associated with neurological and gastrointestinal adverse events and with the rapid emergence of virus resistance [1]. These two agents are effective as therapy for influenza A in immune-competent patients, but the benefit of their use in patients after SCT is uncertain.

The neuraminidase of influenza viruses plays an essential part in allowing virus release from the surface of infected cells by cleaving sialic acid residues of the cell membrane. Neuraminidase inhibitors block the interaction of this enzyme with the sialic acid residues by fitting into the shallow pocket of the neuraminidase active site [36]. The neuraminidase inhibitors are active against both influenza A and B viruses. The prophylactic and therapeutic efficacy of zanamivir and oseltamivir for influenza in otherwise healthy adults has been documented in several randomized placebo-controlled trials [33]. Future studies may help to clarify the role of these agents in the treatment of influenza in SCT recipients.

Because of the limited therapeutic options, the prevention of community respiratory virus infections is of foremost importance after SCT. Infection control measures, including droplet precautions and prompt isolation of infected patients, are associated with a significant re-
duction of nosocomial respiratory virus infections in SCT recipients [55]. Immunization with influenza virus vaccine of patients and hospital personnel before the influenza season has protective effects [13, 55]. Other vaccines are under development, and might further reduce the morbidity caused by community respiratory viruses among patients who have undergone SCT in the future.

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