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REVIEW ARTICLE

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Current concepts and challenges in the prevention and treatment of viral infections in immunocompromised cancer patients

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Abstract Patients with acute leukemia treated with intensive chemotherapy and recipients of bone marrow or peripheral blood stem cell transplants are at high risk of serious viral disease. Recent progress in diagnostic methods and in antiviral drug treatment has permitted the development of efficient management strategies particularly for infections due to herpes simplex virus, varicella-zoster virus, and cytomegalovirus in these patients. By contrast, specific treatment of other virus infections in immunocompromised cancer patients remains an unresolved issue. The emergence of herpesvirus resistance to antiviral drugs is a matter of concern, and its clinical importance among patients with malignancy needs to be elucidated. Future investigations may furthermore help to clarify the role of novel antiviral agents, such as cidofovir, lobucavir, and compound 1263W94, and of the adoptive immunotherapy with virus-specific CTL clones in severely immunodeficient cancer patients.

Key words Bone marrow transplantation · Herpesvirus infection · Antiviral prophylaxis · Antiviral therapy · Adoptive immunotherapy

Introduction

Immunocompromised cancer patients are at elevated risk for serious viral infections. Patients with malignancy who are particularly susceptible to viral disease include those with leukemia or lymphoma, recipients of an allogeneic bone marrow transplant (BMT) or peripheral blood stem cell transplant (PBSCT), and patients treated with high-dose cytoreductive chemotherapy followed by autologous BMT or PBSCT [51, 71]. Both DNA and RNA viruses are important causes of viral disease among profoundly immunodeficient cancer patients (Table 1) [24, 31, 37, 38, 51, 59, 64, 71, 76, 77, 82]. Infections caused by DNA viruses are generally more frequent, which is related to the propensity of these viral agents to establish long-term latency after primary infection and to reactivate during subsequent periods of immunosuppression [51].

A challenging and unresolved issue is the management of infections caused by viruses that do not belong to the family of human herpesviruses. For example, respiratory viruses, such as respiratory syncytial virus and the influenza and parainfluenza viruses, contribute to significant morbidity and mortality in immunocompromised cancer patients [31, 37, 38, 59, 76, 77]. Infections caused by respiratory viruses are characterized by a potential for both community and nosocomial acquisition, high attack rates, and an ability to cause seasonal outbreaks. However, the current diagnostic techniques for these viral agents are of limited clinical value, and there is no specific antiviral therapy of respiratory virus diseases that was proven to be efficacious and safe in severely immunocompromised hosts [59]. At present, no firm treatment recommendations can be made for cancer patients who develop infections caused by respiratory viruses or by other viruses outside the herpesvi-

Table 1 Viruses causing significant morbidity among severely immunodeficient cancer patients

DNA viruses	RNA viruses
Herpes simplex virus types 1 and 2	Respiratory syncytical virus
Varicella-zoster virus	Rhinovirus
Cytomegalovirus	Influenza virus types A, B, C
Epstein-Barr virus	Parainfluenza virus types 1 to 4
Human herpesvirus 6	Measles virus
Hepatitis B virus	Hepatitis A and C viruses
Adenovirus	Rotavirus
Polyomaviruses (JC, BK)	

rus group, and these infections will therefore not be discussed in more detail in this review.

Of the viruses listed in Table 1, herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV), and cytomegalovirus (CMV) have been particularly well studied, and new strategies for the management of disease caused by these herpesviruses in cancer patients were defined [51, 52, 71, 82]. Progress was made possible by the introduction into clinical use of rapid and sensitive diagnostic methods and of potent antiviral drugs against these viruses in recent years (Fig. 1) [51, 52]. By contrast, the clinical role of other members of the human herpesvirus family (Epstein-Barr virus, human herpesviruses 6, 7, and 8) among patients with malignant disorders has only been partially characterized, and efficient antiviral drug therapy for diseases associated with these viruses is not available at this time [9, 10, 13, 15, 16, 68, 79, 83]. Thus, this review will focus on current concepts and challenges in the prevention and therapy of disease due to HSV, VZV, and CMV among profoundly immunodeficient cancer patients.

Herpes simplex virus infection

HSV infection in adult cancer patients results almost exclusively from reactivation of latent virus [42], and prevention of HSV disease is therefore primarily aimed at HSV seropositive patients. In the absence of antiviral drug prophylaxis, the incidence of HSV reactivation among patients receiving induction chemotherapy for acute leukemia or undergoing allogeneic BMT was reported to be in the range of 60–80% [8, 42]. HSV disease in these patients is most frequently observed at mucocutaneous sites, but esophageal HSV infection is also common and occurs in approximately 10% of patients who have symptoms of upper gastrointestinal disease [8, 66].

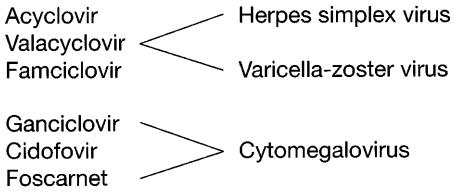

Fig. 1 Antiviral drugs currently available for clinical use against herpesviruses. The drugs are grouped according to their main indications in the prevention and therapy of diseases caused by herpes simplex virus, varicella-zoster virus, and cytomegalovirus. Acyclovir is also used in high doses in the prevention of CMV infection after allogeneic bone marrow transplantation

Three antiviral agents are currently licensed for treatment of clinical manifestations of HSV infection (Fig. 1). Acyclovir became available for clinical use in the early 1980s and has been extensively evaluated since in the prevention and therapy of HSV disease among both immunocompetent and immunocompromised hosts [78]. Prophylactic acyclovir has become a standard of care at many cancer centers for HSV seropositive patients who are treated for hematologic malignancies or who undergo BMT or PBSCT [71, 78]. Recommended dosages for acyclovir prophylaxis are 250 mg/m^2 or 5 mg/kg i.v. every 12 h, or between 200 mg three times daily and 800 mg twice daily when the drug is given orally, and the length of treatment is usually 3–5 weeks after the start of chemotherapy [51]. Acyclovir therapy of established mucocutaneous or esophageal HSV disease in cancer patients is given either i.v. at a dose of 250 mg/m^2 or 5 mg/kg every 8 h, or orally at a dose of 200–400 mg five times daily for a duration of 7–10 days [51, 72, 78]. For therapy of HSV pneumonia or HSV encephalitis, acyclovir i.v. at 500 mg/m^2 or 10 mg/kg given every 8 h for 10–14 days is recommended by some experts, but antiviral treatment of these conditions has not been studied systematically in cancer patients.

More recently, valacyclovir, a prodrug of acyclovir with 3–5 times its oral bioavailability, and famciclovir, the oral prodrug of penciclovir, were introduced and were shown to exert potent inhibitory activity against HSV types 1 and 2, and VZV [4, 60, 69, 70, 75]. A major advantage of these new agents over acyclovir is their high oral bioavailability, which permits less frequent dosing when treating HSV or VZV disease [4, 49, 60, 69, 75]. However, current results documenting the therapeutic efficacy of valaciclovir and famciclovir for these indications are derived from trials among immunocompetent patients, and firm conclusions regarding the antiviral activity of these drugs in immunocompromised cancer patients cannot be inferred from these studies.

Varicella-zoster virus infection

The clinical manifestations of VZV infection are chickenpox and herpes zoster. Chickenpox results from pri-

mary VZV infection and occurs in most cases in children under the age of 10 years. Children with acute leukemia who develop chickenpox are at particularly high risk for VZV pneumonia, which had an incidence of 32% and a fatality rate of 7% in one study [23]. Herpes zoster is due to reactivation of latent VZV and, among cancer patients, is most frequently observed in those with leukemia or lymphoma and in recipients of autologous or allogeneic BMT [12, 39, 40].

For therapy of established chickenpox or herpes zoster in immunodeficient cancer patients, the use of acyclovir i.v. at a dose of 500 mg/m^2 or 10 mg/kg given every 8 h for 7–10 days is the currently recommended treatment of choice [3, 48, 51, 67, 78]. Valaciclovir and famciclovir are being evaluated for therapy of herpes zoster after BMT, but results from these trials have not been reported yet.

Prevention of chickenpox among immunocompromised hosts requires strict isolation from infectious persons. However, isolation procedures may be too late in some instances, because patients with chickenpox can be contagious up to 2 days before the skin rash appears [67]. VZV seronegative cancer patients who have been exposed to infectious individuals may benefit from infusions of VZV hyperimmune globulins if this treament is initiated within 96 h after the exposure [67]. Moreover, immunization with a live attenuated VZV vaccine in seronegative children with leukemia was associated with high seroconversion rates and with a reduction of breakthrough varicella infections and of subsequent herpes zoster [26, 30].

Allogeneic BMT recipients are at risk of VZV reactivation for a prolonged period of time after the transplant [29, 39]. The efficacy of long-term acyclovir prophylaxis was therefore assessed in these patients, but the results obtained indicate that such prophylactic treatment is not advisable, since it only delays the occurrence of herpes zoster and carries the potential for induction of VZV resistance [29, 33, 36, 46].

Cytomegalovirus infection

Patients with acute leukemia who are treated with intensive induction chemotherapy and recipients of an allogeneic or autologous BMT or PBSCT are at elevated risk of developing CMV infection and serious CMV disease, such as interstitial pneumonia. In the absence of efficient antiviral prophylaxis, the incidence of CMV infection among these cancer patients is in the range of 30–50%, and approximately one-third of allograft recipients and 10–20% of autograft recipients with documented CMV infection develop CMV pneumonia, which without specific therapy is fatal in over 80% of cases [21, 43, 54, 71, 80]. A strong independent predictor of CMV disease after BMT is CMV viremia, which was associated with a 5.5-fold increased risk for CMV pneumonia in one series [45]. Furthermore, failure to restore a CD8$^+$ cytotoxic T-lymphocyte (CTL) response specific for CMV after BMT or PBSCT was also recognized to be an important predisposing factor for CMV infection and CMV pneumonia during the first 3 months after transplant [35, 55, 57].

Therapy for established CMV pneumonia after BMT or PBSCT remains a major challenge despite the introduction into clinical use of potent antiviral drugs against CMV in recent years. Single-agent therapy of CMV pneumonia, including intravenous ganciclovir and foscarnet, proved to be generally ineffective in BMT recipients [1, 50]. However, several nonrandomized studies evaluating a combination of intravenous ganciclovir plus high doses of intravenous immune globulins for therapy of CMV pneumonia suggested lower fatality rates than in historical controls [19, 50, 62]. Updated results from these studies showed an average survival rate of about 65% early after completion of this combination therapy, but survival 6 months later was only between 30–40% [82]. Thus, with the best presently available therapy the long-term outcome of CMV pneumonia after BMT remains severe, and emphasis must be placed on the prevention of CMV disease in these patients.

Among CMV seronegative allograft recipients, CMV infection can efficiently be prevented by the exclusive use of seronegative or leukocyte-depleted blood products if the BMT or PBSCT donor is also seronegative [6, 7]. Among CMV seropositive patients or seronegative patients with a seropositive organ donor, one approach to prevention of CMV disease is based on suppressing CMV reactivation by the prophylactic use of antiviral drugs. High-dose intravenous acyclovir was evaluated for this indication after allogeneic BMT and was associated with improved survival compared with that in untreated or placebo-treated patients, but was only partially effective in preventing CMV disease [44, 47]. Ganciclovir is considerably more potent than acyclovir against CMV [22]. Prophylactic intravenous ganciclovir in two placebo-controlled studies of allogeneic BMT recipients resulted in significant reduction of CMV disease compared with controls, but there was no survival advantage for ganciclovir-treated patients, which may be related in part to a higher number of deaths from nonviral infections in these patients [28, 81].

An additional strategy for the prevention of CMV disease in transplant recipients, termed “preemptive treatment”, was recently introduced; it consists in administration of antiviral drugs only to patients with virologically documented CMV infection [18, 27, 63]. This strategy permits the restriction of antiviral treatment to the patients most at risk for CMV disease,

which is particularly important in view of the toxicity associated with the potent anti-CMV agents currently available (Fig. 1). Preemptive treatment with intravenous ganciclovir based on positive CMV cultures was investigated in two controlled trials after allogeneic BMT, and resulted in decreased rates of CMV disease and improved survival [27, 63]. However, 12–13% of patients screened by surveillance cultures in these studies developed CMV disease without prior evidence of CMV infection. The proportion of patients missed by culture-based screening for CMV might be reduced by the use of more sensitive and rapid detection methods, such as the antigenemia assay or the polymerase chain reaction (PCR) in peripheral blood specimens [2, 5, 17, 25]. A first randomized comparison of culture-based and PCR-based initiation of preemptive ganciclovir treatment after allogeneic BMT yielded encouraging results; PCR-monitored patients had a lower incidence of CMV disease and better survival by day 100 after transplant [18].

Because of the toxicity and low oral bioavailability of licensed antiviral agents against CMV, there is a need for alternative drugs for the treatment of CMV disease in immunodeficient cancer patients. Several novel antiviral compounds and modified formulations of known drugs have been developed recently and are being investigated for possible clinical use (Table 2). These new agents share a potent inhibitory activity against CMV and an oral bioavailability that in most cases is superior to that of the presently available anti-CMV drugs.

Immunotherapy

Passive immunization by the administration of (hyper) immune globulin infusions to prevent CMV infection and disease after BMT remains a controversial issue. In view of the unclear benefit and substantial costs of this approach, passive immunization cannot be advocated for routine use after BMT or PBSCT without further studies (for more extended discussion see [41, 51]).

The CMV-specific $CD8^+$ CTL response plays a crucial role in the protection of allograft and autograft recipients from CMV infection and CMV pneumonia during the posttransplant course [35, 55, 57]. Restoration of this cellular immune response in BMT recipients by the adoptive transfer of CTL clones specific for CMV has been shown to be safe [58, 74]. Ongoing studies are aimed at determining the efficacy of this new strategy in the prevention of CMV infection and CMV disease after allogeneic BMT (S.R. Riddell, personal communication).

Table 2 New compounds and formulations with antiviral activity against cytomegalovirus that can be administered orally

Ganciclovir prodrug
Cidofovir prodrug
Lobucavir (BMS-180194)
Adefovir dipivoxil
1263 W94

Herpesvirus resistance to antiviral drugs

The emergence of herpesvirus resistance to antiviral agents in immunocompromised hosts is being reported with increasing frequency [53]. Infections due to drug-resistant HSV, VZV, and CMV have become recognized as a clinically significant problem particularly in patients with the acquired immunodeficiency syndrome, whereas data on the importance of herpesvirus resistance in immunocompromised cancer patients remain limited [14, 20, 32, 34, 56, 65, 73]. A survey among centers affiliated to the European Group for Blood and Marrow Transplantation (EBMT) indicated that antiviral drug resistance of herpesviruses is proven or suspected in a substantial number of EBMT centers (Table 3) [56]. Moreover, most patients with acyclovir-resistant HSV disease or ganciclovir-resistant CMV infection appeared to respond to foscarnet treatment [56]. However, broader use of susceptibility testing to antiviral agents is required for better definition of the incidence and clinical importance of disease caused by resistant herpesviruses in BMT recipients. Future investigations should be facilitated by the development of more rapid and efficient methods for detection of herpesvirus resistance [11, 61]. Furthermore, antiviral drugs with mechanisms of activation that differ from those of acyclovir or ganciclovir need to be investigated further to establish alternative treatment options in BMT or PBSCT recipients with herpesvirus disease resistant to these agents.

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Table 3 Herpesvirus resistance to antiviral drugs among 68 centers of the European Group for Blood and Marrow Transplantation. (Data from [55])

Resistant virus	Centers reporting resistance[a] *n* (%)
Herpes simplex virus	17 (25)
Varicella-zoster virus	3 (4)
Cytomegalovirus	19 (28)

[a] 39 (57%) of the 68 centers observed no herpesvirus resistance

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