Management of viral infections in immunocompromised cancer patients[1]

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Summary

Immunocompromised cancer patients are at elevated risk for serious viral disease. The introduction into clinical use of potent antiviral agents and of rapid diagnostic tests resulted in the development of efficient management strategies for infections due to herpes simplex virus, varicella-zoster virus, and cytomegalovirus. The emergence of herpesvirus resistance to acyclovir, ganciclovir, cidofovir, or foscarnet represents an important challenge. The new neuraminidase inhibitors zanamivir and oseltamivir are efficacious in the treatment of influenza in otherwise healthy adults, and need to be investigated among immunodeficient patients with malignancy. Preliminary data on pleconaril, a first broad-spectrum anti-picornaviral compound, are promising.

Key words: immunocompromised cancer patients; stem cell transplantation; virus infection; antiviral prophylaxis; antiviral therapy; antiviral drug resistance

Introduction

Viral infections are a frequent cause of serious disease among patients treated for leukaemia and among stem cell transplant recipients (SCT) [1–4]. In the past two decades several potent antiviral compounds have become available for clinical use, and efficient management strategies for infections due to herpes simplex virus (HSV), varicella-zoster virus (VZV), and cytomegalovirus (CMV) in immunodeficient cancer patients were established. Moreover, new treatment options have emerged for influenza and picornaviral disease [5, 6].

In recent years, major advances in rapid diagnostic techniques for viral infections have further helped to markedly improve the efficacy of antiviral treatment. Shell-vial cultures, antigen detection assays, and the polymerase chain reaction (PCR) permit the detection of viral infections at an early stage enabling the clinician to make timely therapeutic decisions [3, 7–9].

Herpes simplex virus

HSV types 1 and 2 are a common cause of mucocutaneous lesions in patients with malignancy [9]. HSV infection results in most cases from reactivation of latent virus, thus antiviral drug prophylaxis is primarily given to HSV seropositive patients. Antiviral drug treatment is aimed both at shortening the duration of HSV disease and at preventing the dissemination of HSV to visceral sites which can lead to life-threatening disease.

The antiviral compounds acyclovir, valaciclovir and famciclovir are presently available for the treatment of HSV disease (table 1) [3, 9, 10]. Prophylactic intravenous or oral acyclovir has become a standard of care for HSV seropositive cancer patients during periods of profound immunosuppression [9]. Allogeneic SCT recipients who develop acute graft-versus-host disease usually require a prolonged HSV prophylaxis. Valaciclovir and famciclovir have an oral biovalailability 3–5 times superior to that of oral acyclovir. Although not systematically studied in this setting, oral valaciclovir is commonly used in the prevention of HSV reactivation after SCT. Intravenous acyclovir remains the therapy of choice for severe mucocutaneous or visceral HSV disease in immunocompromised hosts [3, 9, 10]. Oral acyclovir, valaciclovir, or famciclovir may be considered as alternative therapies for less serious manifestations of HSV disease (table 1) [10].

Varicella-zoster virus

The clinical manifestations of VZV infection are chickenpox (varicella) and herpes zoster. Chickenpox results from primary VZV infection and occurs in most cases in children under 10 years of age. Children with acute leukaemia who develop varicella are at particularly high risk for VZV pneumonia which may occur in up to one-third of patients with a fatality rate of about 10% [11]. Herpes zoster is due to reactivation of latent VZV and is most frequently observed among cancer patients with leukaemia or lymphoma and in recipients of autologous or allogeneic SCT [12, 13].

For chickenpox or zoster in immunodeficient cancer patients, the use of intravenous acyclovir is the treatment of choice (table 2) [3, 10]. For the treatment of localised zoster among patients with mild to moderate immunosuppression, high-dose oral acyclovir, valaciclovir or famciclovir are possible alternatives to intravenous therapy (table 2). In a randomised comparative study of famciclovir versus oral acyclovir for treatment of zoster in immunocompromised hosts, the times to healing of lesions and the rates of secondary zoster dissemination were similar in the two groups [14].

Prevention of chickenpox in immunodeficient

patients requires strict isolation from infectious individuals. Following contact with an infected person VZV seronegative patients may benefit from infusions of VZV hyperimmune globulins if administered within 96 hours of exposure [15]. Immunisation with a VZV vaccine is an additional preventive measure. The use of a live attenuated VZV vaccine in seronegative children with leukaemia results in high seroconversion rates and in a reduction of breakthrough varicella and of subsequent herpes zoster [16, 17]. In a series of 15 children after SCT, a VZV vaccine was effective in preventing VZV disease for up to 2 years after immunisation [18]. Among 75 VZV seropositive SCT recipients randomised to receive an inactivated VZV vaccine or no intervention, immunisation was further associated with a better reconstitution of the specific cellular immunity and markedly reduced the severity of zoster [19].

Following allogeneic SCT, VZV reactivation may occur for a prolonged period of time. However, long-term antiviral drug prophylaxis is not advisable in allograft recipients, since it only delays the occurrence of zoster and carries the potential for induction of VZV resistance [3].

Table 1

Recommendations for prophylaxis and therapy of HSV disease in immunocompromised cancer patients.

Indication	drug	route	dosage	duration
HSV prophylaxis				
HSV seropositive patients	acyclovir	i.v.	250 mg/m^2 or 5 mg/kg q 12 h	3–5 weeks after start of chemotherapy
		p.o.	from 3×200 mg/d to 2×800 mg/d	same as above
	valaciclovir	p.o.	2×500 mg/d	same as above
HSV therapy				
Mucocutaneous or oesophageal disease	acyclovir	i.v.	250 mg/m^2 or 5 mg/kg q 8 h	7–10 d
		p.o.	from 5×200 mg to 5×400 mg/d	10 d
	valaciclovir	p.o.	2×500 mg/d	10 d
	famciclovir	p.o.	2×500 mg/d	10 d
Encephalitis, pneumonia	acyclovir	i.v.	10–15 mg/kg q 8 h	14–21 d

Abbreviations: HSV, herpes simplex virus; i.v., intravenously; p.o., orally

Table 2

Recommendations for the treatment of VZV disease in immunocompromised cancer patients.

Indication	drug	route	dosage	duration
Varicella, disseminated mucocutaneous or visceral herpes zoster	acyclovir	i.v.	500 mg/m^2 or 10 mg/kg q 8 h	10–14 d
Localized mucocutaneous herpes zoster	acyclovir	p.o.	5×800 mg/d	7–10 d
	valaciclovir	p.o.	3×1000 mg/d	7–10 d
	famciclovir	p.o.	3×500 mg/d	7–10 d

Abbreviations: VZV, varicella-zoster virus; i.v., intravenously; p.o., orally

Cytomegalovirus

Patients receiving cytoreductive therapy for acute leukaemia and recipients of allogeneic SCT are at high risk for serious CMV disease following primary infection, reinfection, or reactivation of virus. The strongest predictor of CMV infection after allogeneic SCT is the pretransplant CMV seropositivity of the patient, and CMV viremia is a major predisposing factor for CMV pneumonia and gastro-intestinal CMV disease. Failure to reconstitute a CMV-specific CD8+ cytotoxic T-cell response after SCT contributes to the risk for CMV infection [20, 21]. Data on the importance of CMV infection in non-transplant cancer patients are limited. Among adults with acute leukaemia, CMV pneumonia was reported to occur in 2.9% of patients with a case-fatality rate of 57% [4].

CMV pneumonia after SCT is a serious condition which, with the best presently available therapy, is associated with a mortality rate of 45–78% [3, 22]. Thus, major emphasis must be placed on the prevention of CMV disease in patients after SCT. Prophylactic high-dose intravenous acyclovir mediates only partial protection from CMV disease after allogeneic SCT, and is ineffective in autograft recipients [23]. Intravenous ganciclovir prophylaxis results in less frequent CMV disease but not in improved survival [24]. Alternatively, preemptive ganciclovir therapy initiated upon detection of CMV infection is associated with both decreased incidence of CMV disease and better survival after allogeneic SCT when compared to placebo [25]. The preemptive therapy approach furthermore allows to target the patients at highest risk for CMV disease. Preemptive intravenous foscarnet appears as efficacious as ganciclovir in preventing CMV disease after allogeneic SCT, but is associated with significantly less haematotoxicity [26]. The preemptive ganciclovir and foscarnet regimens used in a recent multicenter randomised trial of the European Group for Blood and Marrow Transplantation (EBMT) are listed in table 3 [26]. Results of a retrospective survey suggest that intravenous cidofovir might play a role in the treatment of CMV infection in SCT recipients [22].

Valganciclovir is an oral prodrug of ganciclovir with a tenfold greater bioavailability compared to oral ganciclovir [27]. Systemic ganciclovir exposure achieved with valganciclovir is comparable to that of intravenous ganciclovir [27]. Thus, valganciclovir has the potential to replace intravenous drug treatment in cancer patients who are able to take oral medication. The pharmacokinetics and safety of oral valganciclovir after allogeneic SCT are currently being investigated.

Table 3

Preemptive treatment regimens for CMV infection after allogeneic SCT as used in a randomised comparison of foscarnet and ganciclovir [26].*

Drug	induction treatment**	maintenance treatment**
Foscarnet	60 mg/kg q 12 h i.v.	90 mg/kg once a day i.v. for 5 days per week
Ganciclovir	5 mg/kg q 12 h i.v.	6 mg/kg once a day i.v. for 5 days per week

 * The initiation of treatment was based on CMV detection in blood by antigenemia assay or PCR.
** Duration of induction and maintenance treatment were 14 days each.
Abbreviations: CMV, cytomegalovirus; SCT, stem cell transplantation; i.v., intravenously; PCR, polymerase chain reaction.

Herpesvirus drug resistance

The emergence of resistant herpesvirus strains that cause disease unresponsive to antiviral drugs is reported with increasing frequency in immunocompromised hosts [28–34]. Acyclovir-resistant HSV disease develops in 7 to 14% of SCT patients who are given acyclovir treatment [28, 31, 32]. While CMV resistance to ganciclovir is observed in up to 27% of patient with AIDS receiving long-term ganciclovir therapy, the incidence of drug-resistant CMV infection in cancer patients remains undefined [29, 30, 33, 34]. In the past, intravenous foscarnet was commonly used for acyclovir-resistant HSV disease or ganciclovir-resistant CMV disease, and outcome was favorable in most cases [29]. More recently, the presence of multidrug-resistant HSV or CMV strains was documented in several SCT recipients, and resistance to foscarnet was not infrequent [31–33]. Many clinical isolates are susceptible to cidofovir, and this agent was efficient in some patients with multidrug-resistant HSV disease [31, 32].

Influenza viruses

Influenza A and B viruses are responsible for important morbidity and mortality in profoundly immunocompromised cancer patients [2, 3]. During winter approximately 20% of community respiratory virus infections in adult SCT recipients are due to influenza viruses, and pneumonia develops in approximately two-thirds of these patients with a case-fatality rate of up to 50% [2]. The severity of influenza in cancer patients appears to be related to the degree and duration of immunosuppression.

Amantadine and rimantadine are effective in the treatment of influenza A virus infection in otherwise healthy patients. However, the benefit of the prophylactic or therapeutic use of these compounds in cancer patients is uncertain. The novel neuraminidase inhibitors zanamivir and oseltamivir are active against both influenza A and B viruses. Several placebo-controlled trials have documented the efficacy and safety of neuraminidase inhibitors in the treatment of influenza in immunocompetent adults [5]. Studies are needed to assess the role of these antiviral agents in cancer patients with influenza-like illnesses.

To reduce the risk of nosocomial transmission of influenza viruses, infection control measures and immunisation with influenza virus vaccine of patients and hospital personnel are recommended [35, 36].

Picornaviruses

The family of picornaviruses includes enteroviruses and rhinoviruses. Disseminated enterovirus infections with fatal outcome may occur in patients after SCT [1]. Pleconaril, a first broad-spectrum anti-picornaviral agent, has recently become available for clinical use [6]. This compound is orally bioavailable and achieves high concentrations in the central nervous system and nasal secretions. Preliminary experience with pleconaril for the treatment of life-threatening enterovirus infection is promising, and this drug appears well-tolerated and safe [6]. Among 38 patients, including 4 SCT recipients, who developed enterovirus infections and who received pleconaril as an oral suspension for 7–10 days, a favorable clinical outcome was observed in 78% of the patients, and a virological response was documented in 92% of the cases [6]. Studies of pleconaril in larger populations of immunocompromised cancer patients are warranted.

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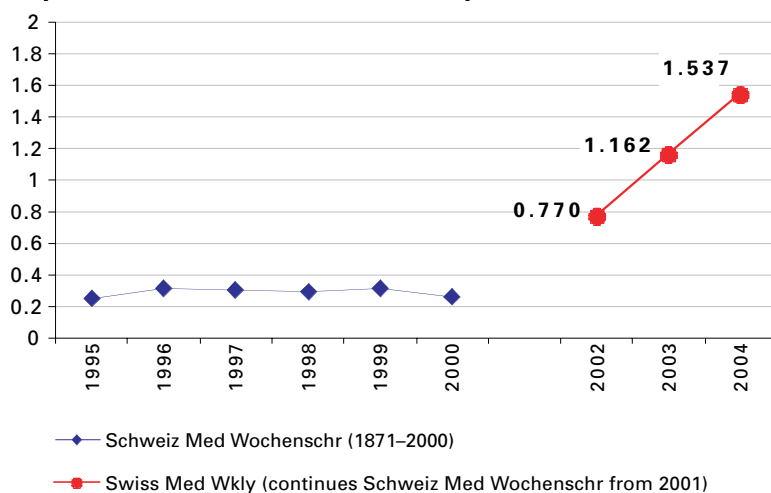- No page charges and attractive colour offprints at no extra cost

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