Antiviral prophylaxis in patients with haematological malignancies and solid tumours: Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Oncology (DGHO)


1Medizinische Klinik, Klinikum Augsburg; 2Klinik I für Innere Medizin, Hämatologie – Onkologie – Infektiologie, Klinikum der Universität zu Köln; 3Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg; 4Klinikum Schwäbisch Gmünd, Zentrum für Innere Medizin; 5Abteilung Hämatologie und Onkologie, Klinik und Poliklinik für Innere Medizin, Universität Rostock; 6Universitätsklinik Freiburg; 7Klinik für Innere Medizin, Klinikum Frankfurt (Oder); 8Medizinische Klinik mit Schwerpunkt Hämatologie und Onkologie, Charité – Campus Virchow Klinikum – Berlin; 9Medizinische Klinik III, Charité – Campus Benjamin-Franklin – Berlin; 10Medizinische Klinik und Poliklinik III, Klinikum der Universität München-Grosshadern; 11Zentrum Innere Medizin – Abteilung Hämatologie und Onkologie, Georg-August Universitäts-Universität; 12Klinikum Johannes Gutenberg-Universität, III. Medizinische Klinik und Poliklinik, Mainz, Germany

Received 31 May 2005; revised 22 September 2005 and 4 December 2005; accepted 5 December 2005

Morbidity and mortality in patients with malignancies are increased by viral infections. These mostly are reactivations of asymptomatic latent infections. They primarily concern clinical entities associated with the reactivation of herpes viruses, such as varicella zoster virus (VZV) and cytomegalovirus (CMV). Respiratory tract infections caused by influenza, parainfluenza or respiratory syncytial virus (RSV) are less common. Since reactivation of latent infections has major clinical impact, antiviral prophylaxis is an attractive approach for patients expecting immunosuppression. The main risk factor for clinically relevant reactivation is profound disruption of cellular immune response. Duration and severity of chemotherapy induced neutropenia are of lesser importance. The risk of viral disease increases with the intensity and duration of functional T-cell suppression. This has been documented specifically with allogeneic stem cell transplantation or of alemtuzumab (Campath-1H) antibody therapy. The objective of this guideline is to review the basis of prophylactic strategies and to provide recommendations for clinicians treating patients with haematological malignancies and solid tumors.

Key words: guidelines, antiviral prophylaxis, solid tumour, infection

introduction

Most viral infections in patients with haematologic malignancies or solid tumours result from reactivation of asymptomatic latent infections, predominantly of herpes viruses, e.g. varicella zoster virus (VZV) and cytomegalovirus (CMV). Exogenous respiratory tract infections caused by influenza, parainfluenza or respiratory syncytial virus (RSV) are less common [1].

The main risk factor for clinically relevant reactivation is profound disruption of cellular immune response. The duration and severity of neutropenia are of lesser importance. The risk of viral disease increases with the intensity and duration of functional T-cell suppression. This has been documented specifically with allogeneic stem cell transplantation or more recently with alemtuzumab therapy [2].

This guideline has been prepared by a panel of experts in the field of infectious diseases in the immunosuppressed host. In a second step it was peer reviewed by a group of leading experts in infectious complications in malignant diseases of the Infectious Diseases Working Party of the German Society for Hematology and Oncology, and approved by the assembly of its members. For this analysis most recent study results have been taken into account, including those presented at major meetings (ASCO, ASH, ECCMID, ESMO, ICAAC) or cited in Medline, Cancerlit, or Cochrane Library) [3].

Strategies for individual patient cohorts are based on their respective risk of viral reactivation or infection and are outlined in the following. The EBM criteria proposed by the Infectious Diseases Society of America (IDSA) are used throughout this document (Table 1). The aim of our recommendations is to aid physicians caring for patients with haematological and oncological diseases in daily clinical decision making.

prophylaxis in conventionally-dosed chemotherapy

Solid tumours do not significantly compromise the cellular immune system. Therefore, patients are at low risk for
Quality of evidence

<table>
<thead>
<tr>
<th>Strength of recommendation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category/grade</td>
<td>A</td>
</tr>
<tr>
<td>Strength of evidence</td>
<td>Good evidence to support a recommendation for use</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Evidence from ≥1 properly randomized, controlled trial</td>
</tr>
</tbody>
</table>

In patients with acute leukaemia, treatment is highly aggressive and consists of a combination of various cytotoxic agents administered in sequential cycles as induction, consolidation and maintenance therapy. Persistent, i.e. >10 days and profound neutropenia (<500 neutrophils/μl) regularly occurs and correlates with the risk of developing fever and infections [4, 5]. Almost all viral infections during neutropenia constitute reactivations of herpes viruses. Treatment of a virus infection may delay treatment of the underlying disease or prevent its continuation.

Table 1. Infectious Diseases Society of America and United States Public Health Service grading system for ranking recommendations [3]

There are good reasons to try to prevent viral diseases. Although several studies demonstrated a reduction in the incidence and severity of oropharyngeal HSV reactivations after prophylactic oral treatment with 800 mg acyclovir [6–12], only one study demonstrated a delay in the onset of fever by approximately 3 days as a benefit of prophylaxis [8]. However, oral acyclovir had no effect on the duration of fever, antibiotic consumption, or incidence of bacteraemia. Lonnqvist et al. likewise detected no effect of antiviral prophylaxis on the duration of febrile neutropenia during AML induction therapy, but identified a reduction in the incidence of gram-positive bacteraemia in the prophylaxis group [13]. None of the available studies demonstrated an effect of antiviral prophylaxis on the initiation of antibiotic treatment, number of febrile days, duration of antibiotic treatment, and onset of opportunistic infections. Therefore, no recommendation for antiviral prophylaxis in patients with acute leukaemia can be given [14].

However, reactivation of chronic hepatitis B in patients undergoing immunosuppressive or antineoplastic treatment is a serious complication. The rate of reactivation is approximately 20–50% in HBsAg positive patients, and can result in fulminant hepatitis [15]. Patients with malignant lymphoma, especially those treated with anthracyclin-containing chemotherapy, are significantly at higher risk as patients with solid tumours [16]. Initiating prophylaxis with the nucleoside analogue lamivudine prior to chemotherapy significantly lowered the rate of HBV activations and hepatitis, compared with a historical control group. This strategy continued for up to 8 weeks after completion of chemotherapy resulted in a significantly lower incidence of cessation of chemotherapy for patients with solid tumours and malignant lymphomas [16]. Another study showed that lamivudine prophylaxis facilitates the completion of chemotherapy and significantly lowers the risk of HBV activation [15, 17]. Patients with positive HBsAg or chronic hepatitis B as well as patients who have already had an episode of HBV reactivation scheduled to receive systemic cancer therapy should receive lamivudine 100 mg qd. The preferable duration of lamivudine prophylaxis is still undetermined. Early termination enhances the risk of HBV activation; excessively long treatment may provoke resistance. Study literature available to date proposes administering lamivudine for 2–3 months after the end of tumour therapy, further monitoring is urgently recommended.

Patients with active malignant disease are at higher risk for upper respiratory tract infection due to influenza, parainfluenza or respiratory syncytiatal virus (RSV). Although response to vaccination with the attenuated influenza vaccine in patients on chemotherapy is highly variable, ranging from 24–75% [18], immunoprophylaxis with the influenza vaccine is recommended for patients with active malignant disease or chemotherapy [19–21]. The same applies to patients with lymphoproliferative disease or multiple myeloma [22, 23]. In areas and seasons where influenza is endemic, chemoprophylaxis with neuraminidase inhibitors can be considered simultaneously to vaccination in exposed patients with a high risk of influenza complications [24].

In conclusion, patients receiving conventionally dosed chemotherapy experience no major T-cell suppression and do not have a higher incidence of invasive primary viral infections. Prophylactic drugs against HSV, CMV and EBV, for example, are not recommended. Strategies against HBV and influenza are summarized in Table 2.

**prophylaxis in severely immunosuppressive chemo-immunotherapy**

Chemotherapy with purine analogues such as fludarabine, 2-chlorodeoxyadenosine (2-CDA) or pentostatin results in major cellular immunodeficiency that may outlast the...
Table 2. Evidence-based recommendations for antiviral prophylaxis in patients with haematological malignancies and solid tumors

<table>
<thead>
<tr>
<th>Underlying malignancy/treatment modality</th>
<th>Conventionally dosed chemotherapy</th>
<th>Severely immunosuppressive chemo-immunotherapy</th>
<th>Autologous stem cell transplant recipients</th>
</tr>
</thead>
</table>
| Hepatitis B
  A II
  Lamivudine 100 mg* | Lamivudine 100 mg* | Lamivudine 100 mg | with CD34 selection |
| Influenza
  B III
  Preseasonal vaccination with attenuated vaccines | Preseasonal vaccination with attenuated vaccines* | Preseasonal vaccination with attenuated vaccines | without CD34 selection |
| HSV/VZV
  C II
  Acyclovir 3–4 × 400 mg p.o. or Valacyclovir 2–3 × 500 mg p.o. | No prophylaxis | No prophylaxis |
| CMV
  A II
  No prophylaxis | No prophylaxis |
| *Risk factors are: second-line therapy, corticosteroids, CD4 < 50/µl, age >65, neutropenia CTC grade III/IV. |
| *Also recommended for rituximab-based chemo-immunotherapy. |
| ‡For all HBs-Ag-positive patients, and for those HBs-Ag-negative patients with positive anti-HBc antibodies who are anti-HBs negative. |

Exposure by months and enhances the risk for viral infections. The CD4+ cell count declines during treatment by a factor of 5–10 to levels ranging from 0 to approximately 300 cells/µl.

Similar T-cell depletion is seen with the monoclonal anti-CD52 antibody alemtuzumab. The CD4+ helper cell count declines to levels below 50/µl after 4 weeks, before very gradually recovering towards the end of treatment [25, 26]. This T-cell deficiency is reinforced by the combination of purine analogues and alemtuzumab with corticosteroids. A recent review of opportunistic infections after treatment with monoclonal antibodies documented an approximately 10–40% incidence in CMV and HSV reactivations [2].

First-line fludarabine treatment of CLL does not significantly increase the incidence of severe opportunistic viral infections [27]. Two large randomized studies evaluating fludarabine in this indication did not find any increase in clinically relevant viral complications [28, 29]. Zoster occurred in 13% and HSV reactivations in 10% of patients on fludarabine treatment. It is of note that half of the herpes zoster reactivations occurred after the end of chemotherapy. More than 95% of these reactivations were readily controlled infections that did not require parenteral therapy or hospitalization [30].

Long-term monitoring of fludarabine recipients disclosed incidence rates of 3.6% for herpes simplex and of 13% for zoster reactivations in CLL patients in remission [31]. The incidence of HSV and VZV reactivation was approximately 10% in a cohort of patients with fludarabine refractory disease. Acyclovir prophylaxis effectively prevented HSV reactivation whereas 47% of patients without prophylaxis developed overt disease [32].

A risk factor analysis of infections in CLL patients who had received fludarabine emphasized the importance of the absolute CD4 cell count. VZV reactivation was observed in 26% of patients with a CD4 count < 50/µl as compared with an incidence of only 6% in subjects with a CD4 count > 50/µl. For herpes simplex reactivation the incidence rates were 16% and 5%, respectively. In a multivariate analysis risk factors for herpes virus reactivation were chemotherapy with purine analogues prior to fludarabine, combination with corticosteroids, CD4 cells <50/µl, prolonged neutropenia with neutrophils <1000/µl, renal insufficiency, and age >65 years [33].

HSV or VZV reactivation can be expected in approximately 10% of patients receiving alemtuzumab. Virus reactivations were found in 14% of patients with fludarabine refractory CLL treated with alemtuzumab. Of these reactivations CMV accounted for 54% and HSV for 46%. The incidence was higher in non-responders [25].

Antiviral prophylaxis may be successful in preventing HSV or VZV in alemtuzumab recipients, as studies by Rai and Lundin demonstrate [34, 26]. An analysis of more than 1500 alemtuzumab recipients reported a 3.6% rate of symptomatic CMV reactivations and infections [35]. The German CLL study group observed a CMV reactivation in seven out of 11 patients during alemtuzumab consolidation therapy [36].

In summary, treatment with purine analogues or alemtuzumab is frequently followed by HSV, VZV, and CMV reactivation. Antiviral prophylaxis with acyclovir or valacyclovir is recommended in patients treated with purine analogues, if at least one of the following risk factors is present:

- Second-line chemotherapy
- Treatment with corticosteroids
- CD4 cell count <50/µl
- Age >65 years
- Prolonged grade III or IV neutropenia

Antiviral prophylaxis is not required in patients receiving first-line fludarabine therapy. If prophylaxis is given, it should be initiated in the first week of therapy and continued until 2 months after completion of therapy. CD4 cell counts should be monitored.

Alemtuzumab should be accompanied by prophylactic acyclovir or valacyclovir, which should be given for at least 2 months after completing treatment. Neither agent has proven advantages over the other [37].
CMV prophylaxis as well as monitoring for CMV reactivation is not recommended because no large randomized trials support this approach (Table 2).

Rituximab (Mabthera®) is a monoclonal anti-CD-20 antibody which leads to a profound depletion of circulating B-cells, thereby not affecting the T-cell mediated immune system. B-cells recover usually within 3–6 months after treatment. But, prolonged administration of Rituximab, e.g. as maintenance treatment over 12 months or longer, may result in a significant decrease of levels of Immunoglobulin M [38] without a significant increase in infectious complication. Therefore, antiviral prophylaxis is not required against HSV, CMV, VZV or EBV. However, patients should be monitored carefully, while the occurrence of opportunistic viral infections with, for example, Parvovirus B19 or JC-papovavirus in the context of Rituximab-based treatment has been reported [39–41].

HBV reactivation is a common event after Rituximab based chemo-immunotherapy. Lamivudine should be given for the time of chemo-immunotherapy plus 2–3 months. Patients should be followed carefully while late reactivations have been observed [42–44].

**prophylaxis in autologous stem cell transplantation**

The risk of opportunistic viral infection after autologous peripheral blood stem cell transplant correlates with the reconstitution of the immune system. Where T-cells are depleted by CD34 selection, the highest risk for viral complications is encountered [45].

Predominantly these are mucocutaneous herpes simplex infections during the transplantation phase and VZV reactivations until reconstitution of the immune system. CMV infections are an especially rare finding, but occur at a much higher rate, if CD34-selected grafts are used. A retrospective analysis disclosed incidences of CMV disease and related mortality rates of 22.6% versus 4.2%, and of 12.9% versus 2.1%, respectively in patients transplanted with and without CD34 selection [46]. The rate of CMV reactivation was as high as 89% after a combined purging strategy involving the anti-CD20 antibody rituximab plus CD34 selection [47].

Oral herpes simplex infections occur during post-transplantation granulocytopenia in less than 1% [48–57]. There are more frequent reports of herpes zoster disease in the post-transplantation period, i.e. between d +30 and the end of the first year. The incidences range from 8% to 20% [48].

Randomized controlled studies of antiviral prophylaxis in post autologous SCT patients are not available. The antiviral prophylactic strategy is thus based upon the presence of risk factors. Antiviral prophylaxis with acyclovir or valacyclovir is recommended in patients undergoing CD34 selected transplantation. This prophylactic regimen should start at the initiation of conditioning and continue until d + 30. Continuation after that period depends on whether CD4 cell count has recovered to levels >200/µl. These levels should be determined monthly. There are no randomized studies demonstrating the effectiveness of this strategy, however.

CMV drug prophylaxis or monitoring for CMV reactivation by PCR or assaying the CMV pp65 antigen is currently not recommended.

Routine acyclovir prophylaxis is not recommended in patients without T-cell depletion. Individual adjustment is recommended in seropositive patients with other risk factors such as CD4 cell count <50/µl, previous treatment with corticosteroids, previous purine analogues, history of recurrent herpes infections, or total body irradiation during conditioning.

The risk of activating hepatitis B or C differs in autologous stem cell transplant recipients. In a retrospective analysis [58], the risk of hepatitis B activation after 2 years was 66% compared with 16% for the risk of hepatitis C activation in the first year. No further activation was observed during the second year. The clinical severity was much greater for hepatitis B than for hepatitis C.

Lamivudine prophylaxis can prevent HBV activation in this setting. HBsAg – positive patients should start with antiviral therapy at the time of initiation of cytoreductive therapy. However, prolonged treatment with lamivudine may result in an increased risk of resistant strains and those patients who might not reactivate HBV would be treated unnecessarily. Whether a deferred approach based on HBV DNA PCR monitoring is advisable cannot be decided on. All patients scheduled for autologous SCT should be screened for HBsAg. Positive patients are monitored in close intervals for a rise in viral load to be treated only in case of HBV-reactivation. But, the frequency of monitoring is poorly defined and this approach is based on an expensive and labor-intensive quantitative assay. Therefore, the optimal strategy in terms of cost-effectiveness and safety cannot be defined yet. The identification of risk factors for HBV reactivation may help to resolve this issue. [59].

In summary, the presence of hepatitis B or hepatitis C is not an absolute contraindication to autologous SCT. Lamivudine is recommended for prophylaxis of hepatitis B reactivation.

Primary prophylaxis through preseasonal vaccination with influenza vaccine is recommended (Table 2).

**prophylaxis in allogeneic stem cell transplantation and chronic graft versus host disease (cGvHD)**

Virus infections and reactivations are more frequent after allogeneic stem cell transplantation (SCT) as T-cell mediated immune responses are suppressed for a prolonged period [60]. Risk factors for infections with CMV, EBV, adenoviruses and other respiratory viruses are ex vivo or in vivo T-cell depletion, unrelated or HLA-mismatched transplants, and severe graft versus host disease (GvHD) [61].

**herpes simplex virus (HSV 1+2)**

The risk of HSV disease after allogeneic SCT without prophylaxis is approximately 80%. This relates almost exclusively to virus reactivations during the first few weeks after SCT during bone marrow aplasia or in the presence of stomatitis [62].
Antiviral prophylaxis is recommended for all HSV seropositive patients because it has been proven to lower the incidence of HSV disease [11, 62]. Routine prophylaxis is not recommended for HSV seronegative patients, including those with HSV seronegative donors [63].

Most studies were conducted with acyclovir [64]. The little data on valacyclovir use in this setting indicate efficacy.

Prophylaxis should be continued until granulocyte recovery or until stomatitis has healed. Prolonged prophylaxis (>30 days) should be considered in patients with acute or chronic GvHD or repeated HSV reactivations prior to allogeneic SCT [63, 65] (Table 3).

**varicella zoster virus (VZV)**

Allogeneic SCT recipients carry a 20–50% risk of developing a zoster. Around 95% are endogenous reactivations that usually occur after 3 to 6 months. Patients with an HLA mismatched donor and under GvHD treatment have a higher risk; this also applies to infectious sequlae later on [66].

VZV seronegative family members and contacts of SCT candidates should be vaccinated against VZV no later than 4 weeks before conditioning begins. Contacts with patients after vaccination must be avoided, especially if post vaccination eczema occurs.

Acyclovir effectively prevents from herpes zoster during transplantation. Most reactivations occur in the post-transplantation period [66]. Extended acyclovir prophylaxis pursued for longer than one year after allogeneic SCT or until the end of pharmacological GvHD prophylaxis and therapy lowers the risk of VZV reactivations later on [67]. The fact that most infections are easily managed argues against a recommendation for extended VZV prophylaxis in patients with no additional risk factors.

Primary varicella infections in allogeneic SCT recipients are associated with high mortality. Therefore, SCT recipients should avoid exposure to people with chickenpox or zoster and, until the incubation period of 2 to 3 weeks is over, to people who have come into contact with chickenpox or zoster patients.

If exposure to persons with chickenpox or zoster occurs, passive vaccination with anti-VZV hyperimmunoglobulin at a dose of 1 ml/kg should be given within 4 days to those patients who have chronic GvHD, are on immunosuppressives, or whose SCT dates back <2 years. However, there are no randomized studies to support the effectiveness of this strategy (Table 3).

**Epstein-Barr virus (EBV)**

The main manifestation of EBV infection after allogeneic SCT is the development of post-transplant lymphoproliferative disease (PTLD) in the presence of reactivated infection. The condition has a very poor prognosis. Although the incidence is low (0.5–2.0%) it may rise as high as 20% in the presence of three or more risk factors. The morbidity risk is highest during the 6 months post SCT [68].

Risk factors for developing EBV-related PTLD are:

- *Ex vivo* T-cell depletion
- Treatment with antithymocyte globulin for preventing or treating GvHD
- Anti-CD3 antibodies for GvHD therapy
- Unrelated or HLA-mismatched transplants

Measures to prevent primary EBV infection include not sharing dishes, foods and towels, i.e. avoiding contact with potentially contaminated body fluids [63].

Biweekly EBV monitoring is recommended in patients with three or more risk factors for developing EBV reactivation and PTLD. A single dose of rituximab should be considered in patients with a very high viral load, i.e. $\geq1000$ genome equivalents/ml, as described by van Esser et al. [69] or a rapidly rising titre.

Other pre-emptive therapeutic options in addition to rituximab include the administration of donor lymphocyte infusions (DLIs) and abrupt discontinuation of the pharmacological immunosuppression to activate an EBV-specific T-cell immune response. However, these measures are associated with triggering severe GvHD (Table 3).

**cytomegalovirus (CMV)**

Forty to seventy percent of the population of developed countries are seropositive for CMV. Without preventive
measures seropositive patients have a 45–86% risk of CMV reactivation, and a 20–30% risk of CMV disease. The risk of CMV transmission is 20–40% in case of a CMV seropositive donor [70–72].

To prevent CMV exposure prior to SCT, sexually active CMV negative patients with a partner who is CMV positive or of unknown CMV status should use condoms in order to reduce the risk of transmission [63].

CMV negative patients with a CMV negative donor and CMV negative patients with a potential stem cell donor of unknown CMV status should receive only CMV negative and/or filtered blood products before and after transplantation [73, 74].

Transfusion of CMV negative blood products to CMV positive recipients and/or donors [75] and prophylactic immunoglobulin administration are not recommended [72].

Prophylactic strategies include prophylaxis and pre-emptive therapy in all patients at-risk, i.e. CMV positive recipients and CMV negative recipients with a CMV positive donor [63]. Such strategies have reduced the risk of CMV disease to 1–3% [76]. Antiviral CMV prophylaxis is not generally recommended because of its toxicity, a delayed CMV specific immune recovery, and an increased incidence of late CMV infections after prolonged ganciclovir treatment. Extended prophylaxis may be considered in severe chronic GvHD, intensive glucocorticoid therapy, and after T-cell depletion [77].

Weekly monitoring of CMV replication by PCR or pp65 antigen detection is recommended to trigger antiviral therapy, as this approach lowers the rate of CMV infections and mortality [76, 78].

Initiation of pre-emptive ganciclovir therapy is recommended after a single positive pp65 antigen test or after two consecutive positive CMV PCR assays. Weekly monitoring should continue for at least 100 days after SCT [63].

In view of an increased risk of delayed CMV reactivations a prolonged monitoring for up to 1 year after transplantation should be conducted in patients with chronic GvHD, prolonged immunosuppression and after T-cell depletion. The same procedure applies to patients having received antiviral treatment for a number of weeks, to recipients of transplantation with reduced conditioning, and to those with GvHD [63, 79, 80].

In a randomized study foscarnet was as effective as ganciclovir, while bearing a lower incidence of treatment-limiting drug side effects [81]. The nephrotoxicity (approx. 25%) of cidofovir has limited its use in the pre-emptive setting, despite a promising response rate of 66% in a retrospective analysis [82]. A prospective study of first-line pre-emptive cidofovir did not confirm these results. Only one out of 21 patients exhibited a sustained response to therapy while 15 patients showed only a short-lived response followed by another CMV reactivation [83].

Once valganciclovir is approved for treating CMV infection in allogeneic SCT, it might replace ganciclovir, thus opening up the perspective of out-patient CMV treatment.

HSV prophylaxis with acyclovir has been performed for more than two decades and results in a non-significant reduction of CMV infections and disease irrespective of the daily dose of acyclovir [84, 85]. Prolonged administration of acyclovir for a period of seven months reduced mortality by 20% compared with the standard of a one-month treatment. In a randomized comparison of valacyclovir and acyclovir for up to 18 weeks after transplantation, valacyclovir was superior in reducing CMV reactivations (28% versus 40%, P < 0.0001). There was no effect on the rates of CMV disease or survival [71]. CMV prophylaxis with acyclovir or valacyclovir is not recommended.

respiratory tract viruses and adenovirus

RSV, parainfluenza-, influenza- and adenovirus infections are associated with severe infections in immunocompromised hosts [86–88]. Primary infection or reactivation of adenovirus manifests as haemorrhagic cystitis or pneumonia. They can only be avoided by exposure prophylaxis before and after SCT [63]. Severe GvHD is considered a risk factor.

For influenza prophylaxis, patients, household contacts and medical staff members should be vaccinated before SCT and at yearly intervals starting 6 months post SCT [63]. Prophylactic antivirals are not recommended.

hepatitis B

HBsAg positive allogeneic SCT are at risk of developing severe and possibly fatal hepatic disease, chiefly sinusoidal obstruction syndrome (SOS) [89].

Anti-HBs negative donors for HBsAg positive patients should be vaccinated before stem cell collection. Treatment with lamivudine is strongly recommended in order to suppress HBV reactivation or hepatitis in HBsAg positive allogeneic SCT recipients; promising case reports have been published and prospective studies are initiated [90, 58].

Transplantation of a HBs-Ag negative patient with stem cells from an HBsAg positive donor is associated with a high risk of transmission, but few patients develop chronic hepatitis B [91]. Anti-HBV therapy with, for example, lamivudine for HBsAg-positive donors and recipients, eventually added by HBV vaccination to HBsAg-negative recipients before SCT has been reported as effective strategy in this setting to reduce HBV-related hepatitis as well as HBV-related hepatic failure [92, 93].

hepatitis C

A cohort study showed that HCV RNA positive patients had a significantly higher risk of developing SOS. Increased ALT was a significant predictor [94].

Transplantation of stem cells from an HCV RNA positive donor is associated with a high transmission rate and should be avoided. However, the incidence of severe hepatic complications does not seem to be elevated and the resulting hepatitis is mild. Risk factors for severe hepatic complications, SOS in particular, include an unrelated donor, and elevated ALT levels in the donor [91]. If there is time enough and no alternative options are available, the potential donor may be treated for at least 6 months with interferon α and ribavirin in keeping with the standard HCV genotype-dependent treatment of chronic hepatitis C.
Viruses associated with various clinical entities in allogeneic SCT recipients are interstitial pneumonia, myelosuppression, encephalitis and hepatitis. However, the correlation between clinical symptoms and detection of HHV-6 is poorly defined. No established prophylaxis exists [88].

parvovirus B19, and the polyoma viruses BK and JC

Viruses associated with various clinical entities in allogeneic SCT patients. However, no established prophylaxis exists for these and no recommendations can be made.

references

34. Lundin J, Kimby E, Björholm M et al. Phase II trial of subcutaneous anti-CDS2 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukaemia (B-CLL). Blood 2002; 100: 769–773.
47. Flihr T, Hess G, Kolte K et al. Rituximab in vivo purging is safe and effective in combination with CD34-positive selected autologous stem cell transplantation for salvage therapy in B-NHL. Bone Marrow Transplantation 2002; 29: 769–775.


