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GUIDELINES

Management of HSV, VZV and EBV infections in patients with hematological malignancies and after SCT: guidelines from the Second European Conference on Infections in Leukemia

J Styczynski[1,9], P Reusser[2,9], H Einsele[3], R de la Camara[4], C Cordonnier[5], KN Ward[6], P Ljungman[7] and D Engelhard[8], for the European Conference on Infections in Leukemia

[1]*Department of Pediatric Hematology and Oncology, Collegium Medicum UMK, Bydgoszcz, Poland;* [2]*Department of Medicine, Hôpital du Jura, Porrentruy and Basel University School of Medicine, Basel, Switzerland;* [3]*Department of Internal Medicine, Wuerzburg University Hospital, Wuerzburg, Germany;* [4]*Servicio de Hematologia, Hospital de la Princesa, Madrid, Spain;* [5]*Department of Hematology, Henri Mondor Teaching Hospital, AP-HP and University Paris 12, Creteil, France;* [6]*Centre for Virology, University College London, London, UK;* [7]*Department of Hematology, Karolinska University Hospital Huddinge, Stockholm, Sweden and* [8]*Department of Pediatrics, The Hebrew University, Hadassah University Hospital, Jerusalem, Israel*

These guidelines on the management of HSV, VZV and EBV infection in patients with hematological malignancies and after SCT were prepared by the European Conference on Infections in Leukemia following a predefined methodology. A PubMed search was conducted using the appropriate key words to identify studies pertinent to management of HSV, VZV and EBV infections. References of relevant articles and abstracts from recent hematology and SCT scientific meetings were also reviewed. Prospective and retrospective studies identified from the data sources were evaluated, and all data deemed relevant were included in this analysis. The clinical and scientific background was described and discussed, and the quality of evidence and level of recommendation were graded according to the Centers for Disease Control criteria.
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Introduction

The recommendations of the European Conference on Infections in Leukemia are based on a review of the English-language literature following a predefined methodology.[1] Literature searches were made to identify studies concerning management of HSV, VZV and EBV infections in leukemia patients and in SCT recipients. As many of the published studies were not properly controlled, but were either observational or used historical controls, drawing firm conclusions proved challenging. Preliminary recommendations were prepared by the writing committee, presented at a consensus conference, and then revised to take account of discussions. The quality of evidence and level of recommendation were graded according to the Centers for Disease Control criteria (Table 1).[2]

Herpes simplex virus (HSV)

Herpes simplex virus types 1 and 2 commonly cause mucocutaneous lesions in patients with hematological malignancies (HSV type 1 more frequently).[3,4] Following primary infection, HSV establishes latency in the neuronal cells of sensory nerve ganglia and may reactivate upon external stimuli and during periods of immunosuppression.[5] Up to 80% of adult patients with leukemia are HSV seropositive. HSV lesions in patients with leukemia result in most cases from reactivation of latent virus, whereas primary infection is unusual.[6,7] HSV reactivation is frequent both in patients with acute leukemia undergoing induction chemotherapy and in SCT recipients. The incidence of HSV lesions among seropositive patients receiving chemotherapy for acute leukemia was 61 and 66%, respectively, in two large series.[3,8] The rate of HSV reactivation among HSV-seropositive allo-SCT recipients was reported to be approximately 80%, with the majority of these infections occurring during the first 4 weeks after transplant.[6] Antiviral drug prophylaxis should thus be given primarily to HSV-seropositive patients. Therapy with antiviral agents 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 conditions.[9]

Correspondence: Professor D Engelhard, Department of Pediatrics, The Hebrew University, Hadassah University Hospital, Ein-Kerem, PO Box 12000, 91120 Jerusalem, Israel.
E-mail: engelhard@hadassah.org.il
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[9]These authors contributed equally to this work.
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Table 1 Evidence-based system used to determine strength of recommendations[2]

Strength of recommendations		
A	Strong evidence for efficacy and substantial clinical benefit	Strongly recommended
B	Strong or moderate evidence for efficacy, but only limited clinical benefit	Generally recommended
C	Insufficient evidence for efficacy; or efficacy does not outweigh possible adverse consequences (for example, drug toxicity or interactions) or cost of chemoprophylaxis or alternative approaches	Optional
D	Moderate evidence against efficacy or for adverse outcome	Generally not recommended
E	Strong evidence against efficacy or of adverse outcome	Never recommended
Quality of evidence-supporting recommendation		
I	Evidence from at least one well-executed randomized trial	
II	Evidence from at least one well-designed clinical trial without randomization; cohort or case-controlled analytic studies (preferably from more than one center; multiple time-series studies; or dramatic results from uncontrolled experiments)	
III	Evidence from opinions of respected authorities on the basis of clinical experience, descriptive studies or reports from expert committees	

Clinical manifestations

In leukemic patients, HSV reactivation is usually associated with localized mucocutaneous disease in the orofacial region (85–90%), and less frequently in the genital area (10–15%).[6,7,10] The diagnosis of oropharyngeal HSV disease by clinical examination can be difficult when severe mucositis is present. Mucositis is common following high-dose chemotherapy or TBI and occurs at the same time as HSV oral disease. Thus, mucosal disease of the oral cavity can often only be attributed to HSV only if the virus is identified by culture or by other rapid detection methods, such as antigen assays or PCR. Another frequent manifestation of HSV reactivation is esophageal disease. In two prospective endoscopic studies of patients with leukemia and other neoplastic disorders who had symptoms of upper gastrointestinal disease, HSV esophagitis was found in about 10% of patients.[3,11] Uncommon HSV disease manifestations are pneumonia (2–3% of patients in the absence of prophylaxis), hepatitis, meningitis, encephalitis and bone marrow suppression.[12–18]

Monitoring and diagnosis of HSV infection and disease

Viral culture is the original method used for the detection of HSV in clinical specimens and usually yields results within 48 h of inoculation. Antigen detection by immunofluorescence assay (IFA) may also be used, but PCR for HSV DNA is becoming the preferred diagnostic tool.

- Serological tests are used for identification of the seropositive patients before the induction chemotherapy or SCT (BII), but are not helpful in confirming the diagnosis of HSV reactivation (DIII).
- The diagnosis of mucocutaneous HSV disease can be suspected on clinical grounds and may be confirmed by appropriate diagnostic techniques (BIII).
- In the presence of severe mucositis following chemotherapy or irradiation, the diagnosis of oropharyngeal HSV disease is difficult and identification of virus by appropriate diagnostic techniques is required (BIII).
- Routine surveillance for HSV reactivation by culture or PCR during chemotherapy or after SCT is not required (CIII).
- PCR for HSV DNA in cerebrospinal fluid is indicated in the diagnosis of HSV meningitis and encephalitis (AII).

Prevention of HSV disease

HSV-seronegative patients.

- Primary HSV infection in patients treated for leukemia is unusual, and antiviral drug prophylaxis is thus not recommended in HSV-seronegative leukemic patients during chemotherapy or after SCT (DIII).

HSV-seropositive patients. Efficient prophylaxis of HSV disease in immunocompromised hosts was made possible by the introduction of acyclovir. Acyclovir is a synthetic nucleoside analog with marked inhibitory activity against HSV types 1 and 2 and VZV.[19] The drug is activated by phosphorylation and converted to acyclovir triphosphate. As conversion to acyclovir monophosphate requires a thymidine kinase encoded by HSV and VZV, acyclovir is preferentially activated in cells infected by these viruses.

Acyclovir prophylaxis of HSV infection was first evaluated among HSV-seropositive SCT recipients; in a placebo-controlled study, i.v. acyclovir, given at a daily dose of 750 mg/m^2 for a period starting 3 days before SCT and continuing for a total of 18 days, abrogated HSV reactivation but 7 of the 10 placebo-treated patients developed culture-positive HSV lesions.[20] In leukemic patients, acyclovir prophylaxis at the same daily dose, administered 1–32 days following chemotherapy, prevented HSV disease in all 14 patients, vs 11 (73%) of 15 patients receiving placebo.[8] The efficacy of acyclovir in preventing HSV reactivation in patients with hematological malignancy was confirmed in several other trials of i.v. or oral acyclovir prophylaxis.[21–24] Prophylactic use of acyclovir has thus become standard treatment at many cancer centers for HSV-seropositive patients receiving chemotherapy for hematological malignancy or undergoing SCT.[9,25,26]

In addition to acyclovir, the newer antiviral compounds valaciclovir and famciclovir are active against HSV.[4,27] Both agents have an oral bioavailability 3–5 times superior to that of oral acyclovir. Although less studied, oral valaciclovir or famciclovir are commonly used in the prevention of HSV reactivation during induction chemotherapy for leukemia and after SCT.[4,28]

- HSV-seropositive patients undergoing allo-SCT for acute leukemia should receive antiviral drug prophylaxis (AI).
- HSV-seropositive patients treated for acute leukemia by chemotherapy alone should be considered for antiviral drug prophylaxis (BIII).
- Intravenous acyclovir 250 mg/m^2 or 5 mg/kg every 12h (AI), oral acyclovir 3×200 to 2×800 mg/day postoperatively (p.o.) (AI), oral valaciclovir 2×500 mg/day p.o. (AII) or famciclovir 2×500 mg/day p.o. (BIII) should be given prophylactically for 3–5 weeks after the start of chemotherapy or after SCT, and for longer periods in children treated for acute leukemia (BIII).

- The i.v. route is preferred in patients who develop chemotherapy- or irradiation-induced mucositis, which impedes intake of oral medication (CIII).
- Allogeneic SCT recipients, who develop GVHD or receive immunosuppressive treatment, including steroids, usually require prolonged HSV prophylaxis (BII).

Therapy of HSV disease. Intravenous acyclovir remains the therapy of choice for severe mucocutaneous or visceral HSV disease in immunocompromised cancer patients.[3,9,19,27] Oral acyclovir, valaciclovir or famciclovir may be considered as alternatives for less serious manifestations of HSV disease.

In a randomized, placebo-controlled trial of i.v. acyclovir therapy for mucocutaneous HSV disease, including various immunocompromised hosts, acyclovir significantly shortened the periods of virus shedding and lesion pain, and induced more rapid lesion scabbing and healing.[12] Intravenous acyclovir was also shown to be effective therapy for mucocutaneous HSV infection among SCT recipients: 13 (76%) of 17 patients receiving acyclovir at a dose of 250 mg/m^2 every 8 h for 7 days had a beneficial response compared with 2 (12%) of 17 given placebo.[29] A subsequent placebo-controlled study documented the efficacy of oral acyclovir therapy, 400 mg five times daily for 10 days, in SCT recipients with mucocutaneous HSV lesions: it significantly shortened the median duration of viral shedding and new lesion formation, and reduced the time to resolution of pain and lesion healing.[30]

- Intravenous acyclovir 250 mg/m^2 or 5 mg/kg every 8 h for 7–10 days is the therapy of choice for severe mucocutaneous or visceral HSV disease (AI).
- Oral acyclovir, from 5×200 to 5×400 mg/day p.o. for 10 days (AI), valaciclovir 2×500 mg/day p.o. for 10 days (BIII) or famciclovir 2×500 mg/day p.o. for 10 days (BIII) may be considered as alternatives for less serious manifestations of HSV disease.
- For HSV pneumonia or HSV meningitis and encephalitis, a higher dose of i.v. acyclovir 500 mg/m^2 or 10 mg/kg every 8 h for 14–21 days should be considered (CIII).

HSV resistance to antiviral drugs. The emergence of resistant HSV strains that cause disease unresponsive to antiviral drugs has been reported in patients with hematological malignancy.[31–42] Interestingly, a long duration of acyclovir prophylaxis is associated with low probability of HSV-resistant disease in SCT recipients.[43]

Resistance to acyclovir is associated with prolonged HSV reactivation, but severe disease is infrequent.[31,32] However, resistant HSV strains have been isolated from immunocompromised hosts who had serious mucocutaneous HSV disease unresponsive to acyclovir, or who had esophagitis, meningoencephalitis or pneumonia due to HSV.[35,37,44–46]

The mechanism of resistance in the vast majority of HSV strains isolated to date was a marked deficiency in viral thymidine kinase resulting in reduced activation of acyclovir in virus-infected cells.[36,44,47,48] Acyclovir-resistant HSV isolates are susceptible to other antiviral agents, such as foscarnet or cidofovir, that do not require viral thymidine kinase for activation.[38,40–46,49] A randomized study comparing foscarnet with vidarabine showed superior efficacy and less frequent toxicity in the group receiving foscarnet.[49] Foscarnet may be used as an alternative treatment for acyclovir-resistant HSV disease in leukemic patients, and should be given with hydration to minimize its potential renal toxicity, especially in those who are exposed to other potentially nephrotoxic agents.[36,50]

More recently, the presence of multidrug-resistant HSV strains was documented in several SCT recipients, including, not infrequently, foscarnet.[38–42] Many clinical strains of the virus are susceptible to cidofovir, and this agent was efficient in some patients with multidrug-resistant HSV disease.[38–42]

- If HSV disease is unresponsive to antiviral therapy given at appropriate dose, resistance testing should be performed (CIII).
- Foscarnet 60 mg/kg every 12 h i.v. or 40 mg/kg every 8 h i.v. for 7–21 days or until complete healing is recommended in case of resistance to acyclovir, valaciclovir or famciclovir (BIII).
- Cidofovir 5 mg/kg once a week for 2 weeks, then once every 2 weeks combined with probenecid and i.v. hydration is recommended in case of resistance to foscarnet (BIII).
- For accessible cutaneous lesions, the addition of one of the following is optional: topical trifluridine 5% ophthalmic solution every 8 h; topical cidofovir gel 0.3 or 1% once daily (CIII).

Varicella-zoster virus (VZV)

Primary VZV infection causes varicella (chickenpox), a common childhood disease. During primary VZV infection, the virus establishes latency in the dorsal root ganglia. Reactivation results in herpes zoster (HZ) ('shingles')—grouped painful vesicular lesions can appear in the distribution of 1–3 dermatomes in the immunocompetent host. After exposure to an individual with VZV infection (varicella or HZ), seronegative leukemia patients and SCT recipients are at risk of developing varicella, which can be very severe.[51] The use of systemic corticosteroid appears to substantially increase the risk of severe or fatal varicella.[52,53] After SCT, the risk of varicella is highest in the first 24 months, or beyond this time if undergoing immunosuppressive therapy and/or having chronic GVHD.

Herpes zoster occurred in 25% of children with acute lymphoblastic leukemia (ALL).[54] Following SCT, before the era of acyclovir, nearly one-half of SCT recipients surviving at least 6 months developed HZ with significant mortality.[55] In several retrospective series, in both children and in adults, VZV-seropositive allo-SCT and autologous SCT recipients carried a 10–68% risk of developing HZ, which usually occurred 3–12 months (median 5 months) after SCT, but may appear years later.[56–75] The cumulative incidence of VZV reactivation at 30 months after cord blood transplantation from unrelated donors was 80%.[76]

The most significant risk for VZV infections following SCT is probably chronic GVHD.[73,77–79] Other risk factors include the pretransplant diagnosis of leukemia[73] and other

lymphoproliferative disorders,[69,80] age >50 years,[81] genotypic nonidentity for HLA between marrow donor and recipient,[82] a myeloablative regimen with TBI,[60,81] busulfan, thiotepa and carboplatin in autologous SCT,[56] CD34+ cell-selected allogeneic and autologous peripheral blood SCT[83,84] and deficiency in both CD4(+) and CD8(+) lymphocytes, measured at day 30 after autologous PBPC transplantation.[68]

Clinical manifestations

Varicella manifests as a generalized, pruritic, vesicular rash. In leukemic patients and in those following SCT, there is a risk of progressive severe varicella characterized by continuous eruptions of lesions and a high fever into the second week of the illness, as well as visceral dissemination, which can cause encephalitis, hepatitis or pneumonia and commonly include abdominal pain (which may precede the rash), nausea, vomiting and diarrhea. There are moderately or profoundly elevated liver aminotransferases and pancreatic enzymes.[85] Hemorrhagic varicella may sometimes occur.[86]

In HZ, grouped painful vesicular lesions appear in the distribution of 1–3 dermatomes in the immunocompetent host. However, in leukemia patients and SCT recipients, HZ may disseminate to several more dermatomes or throughout the whole body, with a risk of visceral involvement, which may prove fatal.[87] This visceral dissemination may sometimes occur without skin vesicles, which makes the diagnosis difficult.[88,89] Elevated levels of liver aminotransferases may be the first sign of reactivation of VZV after SCT.[90] There are several case reports describing severe epigastric pain due to VZV gastritis,[91–93] and other reports of abdominal pain, hepatitis and melena,[94] paralytic ileus and ascites,[95] severe abdominal pain together with inappropriate antidiuretic hormone secretion/hyponatraemia,[96,97] HZ ophthalmicus[98] and meningo-encephalitis.[99,100]

Diagnosis

Culture of VZV is not as easy as for HSV. Tzanck smear cannot differentiate between HSV and VZV.[101,102] Direct immunofluorescent-antibody staining takes only 3 h to perform[103,104] and the SimulFluor direct immunofluorescent-antibody staining assay only 1.5 h.[105]

At present, PCR for VZV DNA is considered the best diagnostic tool because it is very specific and sensitive and can detect viral DNA in vesicle samples, crusts and throat swabs from patients with varicella or HZ.[106,107] PCR can be used for tissue specimens as well.[91,92] VZV encephalitis following SCT is diagnosed by PCR of cerebrospinal fluid.[99,100]

Polymerase chain reaction of blood samples (serum/plasma) can document VZV DNA viremia in SCT recipients with zoster,[108] and quantitative monitoring of circulating VZV DNA may be useful for the diagnosis and for assessing the response to treatment of visceral VZV infections without skin manifestations.[92,93,95,109] PCR can also distinguish vaccine strain from wild-type VZV in clinical specimens.[110,111]

How to minimize the risk of leukemic patients and SCT recipients being exposed to an individual with varicella or HZ

Leukemic patients, SCT candidates and recipients should be made aware of the potential risk of getting varicella, and how VZV is transmitted. The medical team should give advise on precautionary measures to patients and their guardians (AII).[112,113] VZV immunization against VZV is indicated for children with no history of varicella and seronegative family members, household contacts and healthcare workers (BIII). Seronegative individuals most likely to come into contact with the patient during the transplantation should be vaccinated >4 weeks before the start of conditioning (BIII). VZV-seronegative leukemic patients and SCT recipients should avoid exposure to people with varicella or HZ (AII). Although the risk for VZV-seropositive patients is low, it is nevertheless not entirely insignificant.[114] This is especially the case for those who have been immunized against VZV because the immune response to the vaccine is lower than that after chicken pox.[115] Patients should avoid contact with patients with varicella or disseminated zoster, who should be placed under airborne and contact isolation until all lesions are crusted (BIII). Patients should also avoid contact with vaccine recipients experiencing a rash after vaccination (develops in up to 10% of adults and 5% of children within 1 month of immunization), as there is a risk of transmission of the VZV vaccine strain[116] (BIII).

- Leukemic patients and SCT candidates and recipients should be informed about VZV transmission and advised of strategies on how to avoid exposure (AIII).
- Family members, household contacts and healthcare workers known to be VZV-seronegative or children with no history of VZV infection should be given varicella vaccine (BIII). Vaccination of seronegative individuals who may be in contact with the patient during transplantation should be done >4 weeks before start of conditioning (BIII).
- VZV-seronegative leukemic patients and SCT recipients should avoid exposure to people with chickenpox or zoster (AII). The risk for VZV-seropositive patients is low.
- Leukemic patients, before and after SCT, should also avoid vaccine recipients experiencing a rash after varicella vaccine (BIII).
- All patients with varicella or disseminated zoster should be placed under airborne and contact isolation. The isolation should continue as long as the rash remains vesicular and until all lesions are crusted (BIII).

Management of VZV-seronegative leukemic patients and SCT recipients after exposure to varicella or HZ

Transmission of VZV is either by inhalation of respiratory secretion or by direct contact with an individual with VZV disease. VZV transmission by marrow or stem cell products has not been documented. Varicella develops in approximately 90% of susceptible immune competent household contacts to an individual with varicella.[117,118] Following a brief contact with varicella, for example, exposure in a hospital, the reported risk was 22%, and a patient's risk of

contracting varicella was significantly related to how near he/she came to the index patient's room.[119] The usual incubation period is as early as 10 or as late as 21 days after initial contact. The incubation period may be prolonged for up to 28 days in immunocompromised patients, who have been in contact with chickenpox or HZ and hence received zoster immune globulin (ZIG) or varicella-zoster immune globulin (VZIG) as prophylaxis.[2]

In VZV-seronegative patients, who have been in contact with varicella or HZ and hence are potentially contagious, airborne precautions should be instituted 7 days after the first contact and continued until 21 days after the last exposure or 28 days post-exposure if the patient received passive immunization against VZV (AIII).

Type of exposure that necessitates intervention

The types of exposure that put seronegative leukemic and SCT recipients at risk of varicella are face-to-face contact of 5 min or more with a person with varicella or with an immunocompromised patient with disseminated HZ, or intimate contact (touching or hugging) with a person with HZ. Patients residing in the same household as a contagious person or in hospital in the same room or adjacent beds in a large ward are also at risk.[120]

Passive immunization and the role of anti-viral prophylaxis after exposure

In children with neoplastic diseases following contact with a close family member with varicella or HZ, prophylaxis with VZIG, an immunoglobulin prepared from normal donor plasma selected for high titer of VZV antibody, or ZIG, prepared from the plasma of donors convalescing from HZ, significantly reduced the incidence of varicella and attenuated the severity of its course.[121–123]

Passive immunization with i.v. VZIG (at a dose of 0.2–1 ml/kg), or i.m. ZIG, or i.v. normal immunoglobulin (IVIG) (300–500 mg/kg) should be given as soon as possible after exposure (<96 h) to VZV-seronegative leukemic patients on chemotherapy and those receiving steroids (up to 4 weeks after steroids were discontinued). The same applies to VZV-seronegative SCT recipients patients who have chronic GVHD, are on immunosuppressive treatment or whose SCT was less than 2 years ago (AII). Seronegative leukemic patients or SCT recipients should also receive prophylaxis if they are exposed to a VZV vaccinee with varicella-like rash, as it may be contagious[116] (BIII).

However, as ZIG and VZIG are in short supply in some European countries, there is a need for an alternative approach of prophylaxis using an antiviral agent.

The use of antiviral agents for post-exposure prophylaxis in leukemic patients and recipients of SCT is not supported by controlled studies, but uncontrolled experience[124–126] suggests that acyclovir prophylaxis reduces the incidence of varicella and its severity. Valaciclovir, famciclovir or acyclovir should be administered from days 3–21 post exposure. Therapeutic doses (rather than those for prevention of VZV reactivation) are recommended: valaciclovir 1000 mg three times daily for adult >40 kg and 500 mg three times daily for <40 kg body weight (must be >12 years old); famciclovir 250–500 mg three times daily; acyclovir 800 mg five times daily (for children: 20 mg/kg four times daily) (AIII).

- Passive immunization with i.v. VZIG (at a dose of 0.2–1 ml/kg) or i.m. ZIG or IVIG (300–500 mg/kg) should be given as soon as possible after exposure (<96 h) to VZV-seronegative leukemic patients on chemotherapy and those receiving steroids (up to 4 weeks after steroids were discontinued), and to VZV-seronegative SCT recipients, patients who have chronic GVHD, who are on immunosuppressive treatment or whose SCT was within 2 years (AII).
- Where passive immunization is not available, post-exposure prophylaxis with acyclovir (800 mg four times daily; 600 mg/m^2 four times daily for children), valaciclovir (1000 mg three times daily; 500 mg three times daily for <40 kg body weight) or famciclovir (500 mg three times a day) is recommended, starting during 3–21 days after exposure (AIII).
- If a second exposure occurs more than 21 days after a dose of passive immunization or after the administration of the antiviral prophylaxis, a prophylaxis should be readministered (CIII).
- Seronegative leukemic patients or SCT recipients should also receive prophylaxis if they are exposed to a VZV vaccinee having a varicella-like rash (BIII).

The approach to VZV-seropositive patients after exposure

Whereas there is no doubt that post-exposure intervention is needed for VZV-seronegative leukemic patients and SCT recipients, the approach to VZV seropositives is controversial. Reports of 57 immunocompromised patients with reinfection were summarized recently.[114] It seems that the rate of reinfection is very low, although not insignificant. Arguments for the use of passive immunization for VZV-seropositive leukemia and SCT recipients include the theoretical potential for supplementing immunity against VZV. The arguments against include the scarcity of VZIG and ZIG, their cost, the low incidence of reinfection, lack of proven efficacy in VZV-seropositive recipients, the possible adverse effects and discomfort associated with passive immunization.[114]

- Prophylaxis in VZV-seropositive patients is optional (CIII).

How to prevent zoster after SCT

Most SCT recipients are VZV seropositive, following varicella in their childhood or following immunization with varicella vaccine, and are at risk of virus reactivation. There have been several retrospective studies of the use of acyclovir prophylaxis to prevent VZV reactivation in SCT recipients. More importantly, there have been three prospective randomized double-blind placebo-controlled studies. In two studies, oral acyclovir was administered for 6 months after SCT. HZ was prevented during acyclovir administration, but occurred frequently after discontinuation of prophylaxis.[127,128] In the third study, acyclovir significantly reduced VZV infections, when administered for a year after SCT. However, 2 years post-SCT, there was no statistically significant difference in VZV reactivation;

VZV disease mostly occurred in those patients with a continuing need for systemic immunosuppression.[129] Continuation of prophylaxis beyond 1 year in allo-SCT recipients who remained on immunosuppressive drugs led to a further reduction in VZV disease.[81] Therefore, for VZV-seropositive allo-SCT recipients, prophylaxis with oral acyclovir (800 mg twice daily; for children: 20 mg/kg twice daily) or valaciclovir (500 mg once or twice daily) is recommended for 1 year (AII), or longer in the presence of GVHD and immunosuppressive therapy (BII). Prophylaxis in autologous SCT is controversial.

- Determination of VZV IgG serostatus before transplant is recommended for all SCT candidates (AIII).
- Prophylaxis with oral acyclovir (800 mg twice daily) or valaciclovir (500 mg once or twice daily) is recommended for seropositive allo-SCT recipients, for 1 year (AII), or longer in the presence of GVHD and immunosuppressive therapy (BII).
- Prophylaxis in autologous SCT is controversial.

Varicella vaccine

Leukemic children have a 50% incidence of mild-to-moderate adverse effects after receiving the live attenuated varicella vaccine, but have a high degree of protection once an immune response to VZV has developed. In such immunized children, the subsequent incidence of HZ is lower than in children who have had natural varicella.[130] Eight to ten years after vaccination, antibodies are detectable in greater than 90% of leukemic children.[131] Although varicella vaccine is not licensed for routine use in children with malignancies, immunization should be considered when a susceptible child with ALL has been in continuous remission for at least 1 year and has lymphocyte counts greater than 700/μl (0.7×10^9/l) and platelet counts greater than 100×10^9/l (BIII).[120]

There are no data for VZV-seronegative leukemic patients who are candidates for SCT with regard to the benefit of immunization with varicella vaccine. Also, the minimum interval required between immunization and transplantation is not known.

Although there is a report that vaccine administered to 15 patients 12–23 months after SCT was well tolerated without adverse reactions,[132] it is recommended for VZV-seronegative SCT recipients at the earliest 2 years after SCT (CIII), and should be delayed further still in those with chronic GVHD and receiving immunosuppressive therapy (EIII).

Immunizing donors with varicella vaccine was safe, but whether it confers a significant protection to SCT recipients requires further study.[133]

Although initial reports of the administration of heat-inactivated live attenuated varicella vaccine to SCT recipients were encouraging,[134,135] this approach has not yet been further developed.

Treatment

Antiviral treatment halts disease progression and reduces the duration of viral replication.[87,136,137] Moreover, it is highly effective at preventing VZV dissemination and fulminant visceral involvement in SCT recipients.[138,139] Intravenous acyclovir, 500 mg/m^2 every 8 h, is the initial therapy of choice for a varicella-like rash in leukemic patients and SCT recipients. When the infection is controlled, oral antiviral medication is an option for the remainder of the treatment.

There are data on immunocompetent hosts with HZ, showing that antiviral therapy reduces post-herpetic pain, especially in patients 50 years of age or older.[140] A recent consensus meeting with systematic literature reviews supports the use of acyclovir, brivudin (where available), famciclovir and valaciclovir as first-line antiviral therapy for the treatment of immune competent patients with HZ.[141]

There is only one small randomized study in SCT recipients that compared oral with i.v. acyclovir for localized HZ in 27 patients with similar favorable outcome.[142] Another multicentered study under double-blind conditions compared the efficacy of 5 days oral brivudin, one 125-mg tablet every 6 h, vs i.v. acyclovir, 10 mg/kg every 8 h in immunocompromised hosts. There was no significant difference between the treatment groups when analyzed in terms of new lesion formation, increase in the area of rash within the primary dermatome, cutaneous dissemination, infection of mucous membranes or visceral organs or in the time to full crusting of lesions.[143] In a randomized, double-blind, multicenter, controlled study, for the treatment of HZ in 148 patients following SCT, organ transplantation or oncology treatment, 10 days of oral famciclovir, 500 mg three times daily, was found to be equivalent to acyclovir, 800 mg five times daily.[144]

Owing to their simpler dosing schedule, valaciclovir (1000 mg three times daily) or famciclovir (500 mg three times daily) are at present favored for adults, when oral therapy is an option. Brivudin is usually not recommended for leukemic patients, because of its potentially fatal interaction with 5-fluorouracil and other 5-fluoropyrimidines.Varicella-zoster virus disease occurring after 1 year of acyclovir prophylaxis usually responds well to treatment, suggesting that drug resistance is not a major problem. However, when acyclovir resistance is suspected, foscarnet or cidofovir are alternatives for therapy.[145] Recently, there was a description of an acyclovir-resistant VZV infection in a pediatric patient after SCT, who received foscarnet as salvage therapy. A novel thymidine kinase mutation was described, along with a new phenotypic assay for characterizing acyclovir resistance in VZV.[146]

- Patients treated for leukemia and SCT recipients who have a varicella-like rash should be started immediately on i.v. acyclovir 500 mg/m^2 every 8 h (AI).
- Vigilance for the possibility of visceral VZV disease without mucocutaneous manifestations (for example, in cases of encephalitis, pneumonitis or hepatitis) is needed, and i.v. acyclovir 500 mg/m^2 every 8 h should be considered in such cases (AIII).
- Oral valaciclovir (3×1000 mg), famciclovir (3×500 mg), acyclovir (5×800 mg; pediatric dosage: 20 mg/kg four times a day) or brivudin (125 mg once daily; pediatric dosage: 5 mg/kg/day in three divided doses), for 7 days, are alternative options for recipients with HZ stable

localized disease (CII). Brivudin is absolutely contraindicated in patients receiving 5-fluoropyrimidines derivates (EII).
- Therapy (i.v./oral) should be given for at least 7 days and to be continued until 2 days after all lesions are crusted (AI).
- A vesicular rash following exposure to varicella vaccine virus should be treated similarly (BIII).
- Foscarnet (60 mg/kg every 12 h i.v.) or cidofovir (5 mg/kg once a week for 2 weeks, then (if still needed) once every 2 weeks combined with probenecide and i.v. hydration) are alternatives for anti-VZV treatment in a case of acyclovir-resistant VZV infection (AIII).

Epstein-Barr virus (EBV)

The EBV is a DNA virus, also called human herpesvirus 4. With respect to biology, it causes two types of infection: (A) primary (early), mainly in children and adolescents; (B) reactivation of latent infection in immunocompromised patients. Syndromes caused by primary infection include infectious mononucleosis, chronic active EBV infection and X-linked lymphoproliferative syndrome. Most EBV reactivations are subclinical and require no therapy; however, it may be manifest as encephalitis/myelitis, pneumonia and hepatitis. EBV-associated tumors (reactivation syndromes) include lymphoproliferative disease (LPD), Burkitt's lymphoma/non-Hodgkin lymphoma (NHL), nasopharyngeal carcinoma, natural killer (NK)-cell leukemia, Hodgkin's disease, hemophagocytic lymphohistiocytosis and angioblastic T-cell lymphoma. The incidence of EBV-related LPD is related to previous therapy and varies from 0.07% in autologous SCT;[147] 0.45% for matched family donor SCT;[148] 1.4% for mismatched family donor SCT;[148]1.3% after alemtuzumab therapy;[149] 4% after matched unrelated donor SCT;[150] 4.5% after umbilical cord blood transplantation;[151] up to 25% after haploidentical SCT;[152] and 11.7–29% after T-cell-depleted matched unrelated donor.[153]

Patients who received an unrelated or mismatched SCT or T-cell depletion (*in vitro* or *in vivo*) should be regarded as at high-risk group for EBV reactivation. Risk factors for development of post transplant lymphoproliferative disorder (PTLD) include unrelated or mismatched SCT, T-cell depletion, use of ATG or OKT3,[154] and also HLA mismatch/T-cell depletion, EBV serology mismatch between donor and recipient and splenectomy.[150] The higher the number of risk factors, the higher the frequency of EBV reactivation.

Definitions

The recommendations for EBV management in patients with leukemia will be presented using the following definitions:

EBV-DNA-emia: detection of EBV-DNA in the blood.

Primary EBV infection: EBV detected in a previously EBV-seronegative patient.

Probable EBV disease: significant lymphadenopathy (or other endorgan disease) with high EBV blood load, in the absence of other etiologic factors or established diseases.

Proven EBV disease (PTLD or other endorgan disease): EBV detected from an organ by biopsy or other invasive procedures with a test with appropriate sensitivity and specificity together with symptoms and/or signs from the affected organ.

PTLD: heterogenous group of EBV disease with neoplastic lymphoproliferation, developing after transplantation and caused by iatrogenic suppression of T-cell function. Diagnosis of neoplastic forms of EBV-PTLD should have at least two and ideally three of the following histological features: (i) disruption of underlying cellular architecture by a lymphoproliferative process; (ii) presence of monoclonal or oligoclonal cell populations as revealed by cellular and/or viral markers; (iii) evidence of EBV infection in many of the cells, that is, DNA, RNA or protein. Detection of EBV nucleic acid in blood is not sufficient for the diagnosis of EBV-related PTLD.

Prophylaxis of EBV-DNA-emia (EBV reactivation): any agents given to an asymptomatic patient to prevent EBV reactivation in seropositive patient (or when the donor is seropositive).

Pre-emptive therapy: any agents or EBV-specific T-cells given to an asymptomatic patient with EBV detected by a screening assay.

Treatment of EBV disease: agents or other therapeutic methods applied to a patient with EBV (proven or probable) disease.

Diagnosis of EBV reactivation

Early and prospective recognition of EBV-viremia reactivation at a molecular level by RQ-PCR to measure EBV-DNA load is recommended in post transplant high-risk patients (BII).[153,155-158] Although different techniques have been used to assess EBV-DNA load, at present there are no data for the optimal method; however, testing of EBV load in whole blood is preferred in the majority of centers. Owing to technical aspects, it is not recommended to test EBV load in peripheral blood lymphocytes (DIII). Screening for EBV-DNA should start at the day of SCT,[159] and it should last for 3 months with frequency at least once a week in high-risk EBV-PCR-negative patients; longer monitoring is recommended in patients undergoing treatment for GVHD, after haplo-SCT, and in those having experienced an early EBV reactivation[159] (CII). In EBV-DNA-positive patients with rising EBV-DNA load, more frequent sampling might be considered (CII). Strategy should depend on individual assessment of patient. The diagnosis of EBV reactivation should be done on the basis of quantitative data. Regarding threshold value, various data are reported and related to local experience. Mostly, 100 g eq/ml by PCR in whole blood or plasma is used.[160] Present data do not allow to establish threshold value calculation for EBV load for diagnosis of PTLD (or other endorgan EBV disease) in SCT patients. It is also not possible to correlate the peak EBV viral loads with clinical disease manifestations.[160,161]

- Prospective monitoring of EBV-viremia by quantitative PCR is recommended after high-risk allo-SCT (BII).
- Monitoring for EBV-DNA should be done at least once a week for 3 months in high-risk patients; longer

monitoring is recommended in patients with GVHD, after haplo-SCT, and in those having experienced an earlier EBV reactivation (BII).
- Threshold value calculation for EBV load for diagnosis of PTLD in SCT patients should be performed on the basis of local data (CIII).

Prevention of EBV reactivation

Reactivation of EBV is common after allo-SCT, but rarely causes significant problems through direct viral end-organ disease. The important complication of EBV replication is PTLD. High-risk patients should be tested for EBV serology before allo-SCT (AII). If a patient is found to be seronegative, the risk of PTLD is higher. Also, SCT donors should be tested before transplantation for EBV serology, particularly in mismatched donors or when T-depletion is planned (AII). When there is a choice, the selection of seronegative donor might be beneficial, as EBV might be transmitted with the graft (BII). CD34-positive selection does not prevent EBV-PTLD.[162] The risk in HLA-identical sibling transplant recipients not receiving T-cell depletion is low, and no routine screening for EBV is recommended (DII).

For patients with hematological malignancies on standard chemotherapy and in autologous SCT recipients, EBV infection is of small importance. No routine diagnostics for EBV are recommended in these groups of patients, both before and after therapy (DIII). However, additional risk factors, such as alemtuzumab treatment (and possibly use of fludarabine, other nucleoside analogs or infliximab), might cause prolonged immunosuppression up to 6 months, causing higher risk of EBV reactivation. The use of alemtuzumab *in vivo* in the nonmyeloablative conditioning might have resulted in the delay in EBV-specific T-cell recovery and increased virus infections.[163]

Poor or negative data are available regarding EBV prophylaxis. Prevention of EBV reactivation in allo-SCT recipients cannot be based on antiviral prophylaxis. Ganciclovir can reduce EBV replication, but neither ganciclovir/foscarnet nor cidofovir therapy/prophylaxis have any impact on the development of EBV-PTLD, so antiviral agents are not recommended (EII). In case of high EBV load, B-cell depletion before allo-SCT (CIII)[164] or prophylactic use of rituximab early after allo-SCT (CIII) are optional. Immune globulin for prevention of EBV reactivation or disease is not recommended in patients undergoing SCT (DIII). Routine antiviral prophylaxis for EBV is not recommended in autologous SCT setting and in other therapies (EIII).

- Allo-SCT recipients should be tested for EBV serology (AII).
- SCT donors should be tested for EBV serology, particularly in mismatched donors or when T-depletion is planned (AII).
- Antiviral agents are not recommended for EBV prophylaxis (EIII) and antiviral prophylaxis have no impact on the development of EBV-PTLD (DIII).
- Immune globulin for prevention of EBV reactivation or disease is not recommended (DIII).
- Routine anti-EBV antiviral prophylaxis is not recommended in auto-SCT setting and in other therapies for hematological disorders (EIII).

Pre-emptive therapy

The occurrence of EBV-PTLD following SCT is relatively rare, but mortality is high in this disease. Owing to an increase in frequency of alternative donor SCT, including T-cell depletion, the risk of development of EBV-DNA-emia is higher than it used to be even several years ago. Response to present therapies for PTLD is poor, thus the therapeutic idea is to prevent the disease in patients at high risk of EBV reactivation. This can be done by: early detection on the basis of precise screening in EBV-DNA-negative patients, frequent monitoring of EBV load in PCR-positive patients and preemptive therapy in patients with rising EBV-DNA-emia.

There are insufficient data for preemptive therapy for EBV-PTLD in patients with EBV-DNA-emia with respect to leukemia, and most data are obtained from patients with PTLD with various initial diagnoses. Prospective monitoring of EBV-viremia is recommended in high-risk patients after allo-SCT (BII), and these patients should be closely monitored for symptoms and/or signs attributable to EBV and PTLD (BII). The following preemptive therapies are recommended after high-risk allo-SCT: (i) rituximab 375 mg/m^2, weekly doses (AII),[159,165] the number of doses should be assessed locally on the basis of changes in EBV-DNA load; (ii) reduction of immunosuppressive therapy, if possible (BII);[166] (iii) donor EBV-specific CTL infusion, if available (CII).[167–169] Response to preemptive therapy could be identified by a decrease in EBV-DNA load of at least 1 log of magnitude in the first week of treatment.[155,170] Emerging problem is related to downregulation of CD20 expression on PTLD cells following repeated therapy with anti-CD20 MoAbs, causing refractoriness to rituximab treatment due to lack of CD20 expression. For other hematology patients, routine monitoring and preemptive therapy is not considered necessary (DIII).

- High-risk patients after allo-SCT should be closely monitored for symptoms and/or signs attributable to EBV and PTLD (BII).
- The risk in HLA-identical sibling transplant recipients not receiving T-cell depletion is low and no routine screening for EBV is recommended (DII).
- No routine diagnostics for EBV before and after SCT are recommended in auto-SCT setting and in other therapies for hematological disorders (DII).
- Routine monitoring and preemptive therapy are not considered necessary in other hematology patients (CIII).
- For preemptive therapy for EBV-PTLD after SCT: anti-CD20 therapy (rituximab) (AII), reduction of immunosuppressive therapy (BII) or donor EBV-specific CTL infusion (CII) are recommended. Usually 1–2 doses of rituximab are sufficient to reduce the EBV-DNA load.

Diagnosis of EBV disease

Diagnosis of LPD or PTLD must be based on symptoms and/or signs consistent with lymphoproliferative process

developing after SCT, together with detection of EBV by an appropriate method applied to a specimen from the involved tissue (AII). Definitive diagnosis of EBV-PTLD requires biopsy and histological examination (including immunohistochemistry or flow cytometry for CD19+ and CD20+). It is important to remember that CD20 can be downregulated on lymphoma cells after therapy. EBV detection in biopsy specimen requires detection of viral antigens or *in situ* hybridization for the EBER (Epstein–Barr-encoded RNA) transcripts (recommendation A).

- Definitive diagnosis of LPD or PTLD must be based on symptoms and/or signs consistent with PTLD together with detection of EBV by an appropriate method applied to a specimen from the involved tissue (AII).

Treatment of PTLD

The following first-line treatment of PTLD is recommended: (i) anti-CD20 therapy (rituximab) (AII);[151,171–173] (ii) reduction of immunosuppressive therapy, if possible (BII); (iii) adoptive immunotherapy with *in vitro*-generated donor EBV-cytotoxic T-cells, if available (CII);[168,174] and (iv) infusion of donor lymphocytes (DLI) to restore T-cell reactivity (CIII). Generally recommended both for preemptive and symptomatic therapy is the use of anti-CD20 MoAbs, in spite of lack of randomized trials. In the 'era of rituximab,' this is a recommendation of highest priority, while other options should be taken into account, when available or as a second-line therapy. The use of EBV-specific CTLs has been shown to be safe and efficacious in the SCT setting, both prophylactically and for the treatment of established PTLD;[167,168] however, there are disadvantages with this approach, such as laborious process, that takes up to 8–10 weeks to generate CTLs, and a high risk of acute or chronic GVHD after CTL therapy. More monitoring of immune function is required in patients with EBV reactivation.

Second line of recommended therapy include chemotherapy (CIII) or hydroxyurea monotherapy (CIII). Antiviral agents are not recommended for PTLD therapy (EIII). Antiviral agents acyclovir and ganciclovir can reduce EBV replication, but are not active in PTLD (EIII). EBV is resistant to the antiviral agents, such as ganciclovir, presumably because of low levels of viral thymidine kinase expression during lytic phase, and lack of expression during latency and IGIV have no impact in PTLD (DIII).

- Anti-CD20 antibodies (rituximab) (AII), reduction of immunosuppression (BII), DLI (CIII) or adoptive immunotherapy with EBV-CTL (CII) are recommended as first-line therapy for PTLD. Usually 4–8 doses of rituximab are needed to obtain clinical improvement and to reduce the EBV-DNA load.
- Chemotherapy is recommended as a second-line therapy (CIII).
- Antiviral agents (EIII) and IGIV (DIII) are not recommended in PTLD.

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