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Recommendations for management in diagnostics and therapy in herpesviruses infections in children with malignancy or after hematopoietic cell transplantation

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Abstract

Herpesviruses infections are serious complications of therapy in patients after hematopoietic cell transplantation (HCT). Development of infection can demonstrate a life-threatening course, abrogating the effect of previous therapy and contributing to a dismal outcome of underlying disease. Representatives from all the transplant centers belonging to the Polish Society of Pediatric Oncology and Hematology have prepared recommendations for a strategy of diagnostic and therapeutic management of herpesviruses infections in children.

This paper presents current recommendations for patients in immune suppression treated in Polish pediatric hematology and HCT centers and is partly based on ECIL 2007–2019 guidelines. It includes detailed guidelines for first- and second-line targeted therapies for CMV, EBV, HSV, VZV, HHV-6, HHV-7 and HHV-8, as well as principles of recommended dosing of antivirals.

Keywords: hematopoietic cell transplantation, children, viral infections, herpesviruses, diagnosis, treatment

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Introduction

Infections with herpesviruses are serious complications after hematopoietic cell transplantation (HCT). Negative impacts of herpesviruses infections such as graft dysfunction, acute rejection or graft-versus-host disease (GVHD) have been reported [1]. The estimated incidence of clinically significant herpesvirus infections in Poland is higher in pediatric than in adult patients: for CMV (28.9% *vs.* 24.7%) and for EBV (19.4% *vs.* 1.9%) [2]. Similar trends have been seen worldwide, although over the past 20 years significant improvements in diagnostics and classification of herpesviruses infections have been achieved, followed by clinical introduction of antiviral drugs and other therapies. Nevertheless, herpesviruses remain one of the most frequent causes of infections in this patient population.

Group members of the Polish Society of Pediatric Oncology and Hematology aimed to provide clinicians with the best up-to-date guidance for their everyday working practice. The aim of this paper was to provide comprehensive guidelines for the management of herpesviruses infections in children with malignancy or after hematopoietic cell transplantation.

Methods

We the authors are members of the Polish Pediatric Group for Hematopoietic Cell Transplantation as a part of the Polish Society of Pediatric Hematology and Oncology. We decided to prepare guidelines outlining the management of herpesviruses in patients treated in hematology, hematopoietic cell transplantation, and pediatric hematology and oncology departments in Poland. Recommendations for children treated in oncology/hematology and/or HCT centers have been prepared based on current European recommendations from ECIL in CMV [3], EBV [4], HHV-6, HHV-7, HHV-8 [5], HSV [6], and VZV [6] supplemented by literature from the last 15 years, depending on when was the most recent update of recommendations. The specificity of the Polish healthcare system was taken into account. Our recommendations have been graded according to the modified system of recommendations of the Polish Society of Pediatric Oncology and Hematology and the Polish Society of Hematology and Blood Transfusion [7] (Tab. I).

Table I. Recommendations with grading system

Strength of recommendation	Definition
Grade A	Strong support of a recommendation for use
Grade B	Moderate support of a recommendation for use
Grade C	Marginal support of a recommendation for use
Grade D	Support for a recommendation against use
Quality of evidence (QoE)	**Definition**
Level I	Evidence from at least one properly designed randomized controlled trial (orientated on primary endpoint of trial)
Level II	Evidence from at least one well-designed clinical trial (including secondary endpoints), without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

Cytomegalovirus

Human cytomegalovirus (CMV), also known as human herpes virus 5 (HHV-5), together with animal cytomegalovirus, belongs to the Herpesviridae family, subfamily beta-herpesviridae, genus Cytomegalovirus [8, 9]. The CMV name is derived from the fact that it causes enlargement of the infected cell (cytomegaly) and induces characteristic inclusion bodies [8]. In the blood, it is predominantly cell-associated, above all with granulocytes and macrophages [8]. CMV infection and disease are important causes of morbidity and mortality in transplant recipients [10], especially after allogeneic hematopoietic cell transplantation (allo-HCT).

Clinical symptoms

During early infancy, CMV determines a primary clinical or subclinical infection, remaining subsequently in a latent state in several types of leukocytes (lymphocytes, monocytes, dendritic cells) as well as in CD34 + cells [11]. This latent state is controlled by T-cell immune effector cells [11]. Primary infection with CMV in overall healthy individuals is usually asymptomatic, or manifests as mononucleosis-like syndrome or a self-limited febrile sickness. Severe and prolonged lymphocytopenia and T-cell dysfunction associated with allo-HCT can cause CMV reactivation, systemic viral infection, and ultimately end-organ diseases such as pneumonitis, colitis, and retinitis [11].

In a non-transplant setting, CMV is a rare disease, not only in patients with solid tumors but also those with lymphoid malignances during intensive chemotherapy [12, 13], and manifests as unexplained fever, fatigue, visual disturbances (retinitis), pneumonia, gastrointestinal disease and encephalitis [12, 14].

Definitions

The definitions on CMV infection and CMV disease in transplant patients were recently revised [9, 10, 15] and include:

- CMV infection — detection of virus nucleic acid or viral proteins (antigens) or virus isolation in any fluid of body or tissue specimen.
- CMV replication — evidence of viral multiplication; sometimes used instead of CMV infection.
- Primary CMV infection — first detection of CMV infection in an individual who has no evidence of CMV exposure.
- Recurrent CMV infection — a new CMV infection in a patient with previous evidence of CMV infection in whom virus has not been found for at least four weeks during active surveillance. Recurrent infection may be a result of reactivation of latent virus (endogenous) or reinfection (exogenous).
- CMV reinfection — detection of a CMV strain that is distinct from strain that caused initial CMV infection.
- CMV reactivation — is likely if two viral strains (prior and current) are found to be indistinguishable, either by sequencing of specific regions of viral genome or by use of a variety of molecular techniques that examine genes known to be polymorphic.
- Symptomatic CMV infection — is diagnosed in patients developing symptoms (fever with or without bone marrow suppression) and who have CMV virions, antigens, or nucleic acid detectable but with no sign of CMV end-organ disease.
- CMV disease — is diagnosed in a patient with symptoms and/or signs from affected organ together with detection of CMV by a test with appropriate sensitivity and specificity from an organ in a biopsy sample or samples from other invasive procedures. CMV retinitis is an exception, for which typical findings from ophthalmological examination are sufficient.
- CMV 'prophylaxis' — use of antiviral agent in a patient to prevent a primary, reactivated, or recurrent CMV infection.
- CMV 'preemptive therapy' — use of antiviral agent for a patient with an asymptomatic CMV infection detected by a screening assay.

Risk factors

Groups of patients at risk of CMV recurrence [9]:

- recipients of immunosuppressive therapies such as HCT (risk in allo-HCT is higher than auto-HCT) and solid organ transplantation, graft-versus-host disease (GVHD) treatment after allo-HCT;
- recipients of immunosuppressive drugs such as anti-CD52, anti-CD20, anti-CD25, anti-tumor necrosis factor (TNF);
- patients with primary immunodeficiencies;
- patients with secondary immunodeficiencies caused by disease of immune system such as hematological malignancy (especially leukemias), human immunodeficiency virus (HIV) infection;
- other patients on hemodialysis and neonates (due to immaturity of immune system).

In the allo-HCT setting, the CMV-IgG serostatus of the donor (D) and recipient (R) before transplantation significantly influences the incidence of CMV recurrence. The highest, 35.8%, risk of CMV infection is when a seronegative donor (D–) is matched for a seropositive recipient (R+), contrary to other matches [D+/R+ (32.1%), D+/R– (12.9%), D–/R– (3.2%)] [9].

Diagnostics

Non-transplant patients and patients before hematopoietic stem cell transplantation

The CMV IgM and IgG serostatus of all pediatric patients with malignancy should be assessed at diagnosis (AII). In pediatric hemato-oncology patients, testing for CMV-DNA should be performed in cases of suspicion of CMV disease (especially with retinitis, non-resolving pneumonia, or prolonged (more than seven days) febrile neutropenia. We recommend this testing especially if symptoms are associated with lymphopenia (AIII) [16].

Both the patients undergoing HCT and the donors should be tested for the presence of CMV IgG antibodies shortly before the transplantation procedure (AII) [3, 17]. The recent guidelines of ECIL-10 recommend PCR testing for CMV before HCT (BII) [18].

After hematopoietic stem cell transplantation

Allogeneic HCT recipients should be monitored for cytomegalovirus in plasma or whole blood (AII), preferably using the PCR technique [3, 17]. Monitoring should be done at least weekly for the first 100 days after the transplant (AII) [3, 17].

Longer CMV monitoring, beyond day +100 after HCT, is recommended (AIII) in patients:

- with acute or chronic GVHD,
- with previous cytomegalovirus reactivation,
- having undergone mismatched or cord blood, or haploidentical HCT (without post-transplant cyclophosphamide),
- on long-term effective prophylaxis,
- displaying persistent immunodeficiency.

Cytomegalovirus DNA cut-off values for pre-emptive therapy should be adapted according to the monitoring technique used and the type of transplantation (AIII) [3, 17, 19].

Choice of HCT donor based on CMV serological status

For a CMV seronegative recipient, a CMV seronegative donor should be chosen (AI, haplo AIII). In the setting of unrelated allo-HCT with myeloablative conditioning for a CMV seropositive recipient, a CMV seropositive donor should

be chosen when possible (BII). For a CMV seropositive recipient undergoing non-T-cell depleted haplo-HCT with post-transplant cyclophosphamide, a CMV seropositive or seronegative donor is suitable (BII) [3, 20–33].

Prophylaxis

Letermovir for 12 weeks after allo-HCT is recommended as a first-line prophylactic drug in CMV-seropositive recipients (AII) [34]. Letermovir is not registered in patients <18 years, and data on letermovir dosing in this age group is still limited [35] (Tab. II). With high efficacy and safety, other drugs used in prophylaxis have a lower grade of recommendation *i.e.* valacyclovir (CI) [3, 36–38], acyclovir (CI) [3, 36, 39], gancyclovir (CI) [3, 40, 41], and valgancyclovir (CII) [3, 42, 43].

Currently, maribavir (DII) [3, 44], brincidofovir (DII) [3, 45], foscarnet (DII) [3, 46, 47], intravenous immunoglobulins (DII) [3, 48, 49] and specific anti-CMV hyperimmune intravenous immunoglobulins (DII) [3, 49, 50] are not recommended for prophylactic use.

Treatment

First-line preemptive therapy

Data on preemptive therapy of asymptomatic patients is available for allo-HCT patients. The decision on preemptive antiviral therapy for prevention of CMV disease should be based on detection of CMV DNA or CMV antigen in plasma or whole blood (AI).

Gancyclovir or foscarnet can be used for the first-line preemptive therapy (AI). Also, valgancyclovir can be used as first-line preemptive therapy, except in patients with gastrointestinal GVHD (AII). The duration of preemptive therapy should be at least 14 days confirmed by one negative test (BIII) [3, 51–55]. No recommendation for letermovir use in therapy can be made.

Second-line preemptive therapy

If possible, reduction of immunosuppressive therapy should be carried out for all second-line and third-line preemptive therapies (BIII). Foscarnet and gancyclovir (or valgancyclovir) can be alternatively used for second-line preemptive therapy (AII). Also, cidofovir can be used as a second- or third-line preemptive therapy (BII). Currently intravenous immunoglobulins are not recommended for second- or third-line preemptive therapy (DIII) [3, 56–65]. In patients ≥12 years and weight ≥35 kg with refractory or resistant CMV, maribavir is also recommended (AII), though it has no current role in CMV prevention [66, 67]. Maribavir is not recommended when encephalitis, meningitis, or retinitis is of concern, since it has poor penetration into the eye and central nervous system (DII) [18].

Treatment of CMV disease

Intravenous gancyclovir is recommended as a first-line therapy (AII). If gancyclovir is not indicated (*e.g.* due to CMV resistance or gancyclovir side effects), foscarnet is recommended (AIII). For second- and third-line therapy, cidofovir or foscarnet with gancyclovir at full dose can be used (BII). Oral valgancyclovir can be used instead of intravenous valgancyclovir, except for patients with gastrointestinal GVHD (BIII). For CMV pneumonia, the addition of immunoglobulin or hyperimmune globulin may be considered (CIII). In manifestations other than pneumonia, immunoglobulins are not recommended (DIII). For CMV retinitis, gancyclovir or foscarnet intravitreal injections can be used combined with general antiviral therapy (BII) [3, 68–72].

Antiviral drug doses used in CMV therapy are summarized in Table III.

Table II. Letermovir oral dosage depending on age [35]

Age group	Dosing with simultaneous cyclosporine intake	Dosing without simultaneous cyclosporine intake
Adult patients	1 × 240 mg/day	1 × 480 mg/day
Pediatric patients		
>30 kg	1 × 240 mg/day	1 × 480 mg/day
18–30 kg	1 × 120 mg/day	1 × 240 mg/day
<18 kg	1 × 60 mg/day	1 × 120 mg/day

Refractory and resistant CMV infection and disease

In cases of clinical resistance to the therapy, the drug should be switched to another anti-CMV active drug (AII) with simultaneous testing to the most frequent CMV mutations (AIII) (Tab. IV).

The definitions of refractory CMV infection or CMV disease include [15]:

- Refractory CMV infection: defined as CMV viremia (DNAemia or antigenemia) that increases (*i.e.* >1 $\log_{10}$ increase in CMV DNA levels in same blood compartment from peak viral load as measured in same laboratory and/or with same commercial assay) or persists (≤1 $\log_{10}$ increase or decrease in CMV DNA levels) after at least two weeks of appropriate antiviral therapy. This definition includes also previously used term 'probable refractory infection'.
- Refractory CMV end-organ disease: defined as a worsening in signs and symptoms or progression to end-organ disease (for a patient not previously diagnosed with CMV end-organ disease) OR lack of improvement in signs and symptoms after at least two weeks of appropriately dosed antiviral therapy. This definition includes also previously used term 'probable refractory end-organ disease'.

These definitions have some limitations: in certain CMV end-organ diseases (*e.g.* CMV gastrointestinal disease or CMV retinitis), the virus may replicate/persist locally at tissue sites and may not be recovered for resistance testing [15].

Table III. Antiviral drugs used for preemptive therapy or therapy of CMV disease. Based on [3, 66, 67, 73]

Drug	Preemptive therapy		CMV disease	
	Dose	Duration	Dose	Duration
Gancyclovir	2 × 5 mg/kg/day *i.v.* 1 × 5–6 mg/kg/day *i.v.*	≥2 weeks (induction) Maintenance until PCR negativity is documented	2 × 5 mg/kg/day *i.v.* 1 × 5–6 mg/kg/day *i.v.*	>3 weeks (induction) Maintenance can be considered
Valgancyclovir*	7 × BSA × creatinine clearance with upper limit of creatinine clearance of 150 mL/min *p.o.* daily (max dose 1 × 900 mg/day *p.o.*) Maintenance — no data	≥2 weeks (induction)	7 × BSA × creatinine clearance with upper limit of creatinine clearance of 150 mL/min *p.o.* daily (max dose 1 × 900 mg/day *p.o.*)	>3 weeks (induction) Maintenance — no data
Foscarnet	2 x 60 mg/kg /day *i.v.* 1 x 90 mg/kg/day *i.v.*	≥2 weeks (induction) Maintenance until PCR negativity can be considered	3 × 60 mg/kg/day *i.v.* 2 × 60 mg/kg/day *i.v.* or 1 × 90 mg/kg/day *i.v.*	>3 weeks (induction) Maintenance can be considered
Cidofovir**	1 × 5 mg/kg/week *i.v.* 1 × 3–5 mg/kg/every two weeks *i.v.*	At least three doses Maintenance until PCR negativity can be considered	1 × 5 mg/kg/week *i.v.* 1 × 3–5 mg/kg/every two weeks *i.v.*	At least three doses Maintenance until PCR negativity can be considered
Maribavir***	Currently not indicated for CMV prevention		2 × 400 mg/day *p.o.*	Total daily dose of 800 mg for eight weeks. Treatment duration may need to be individualized based on clinical characteristics of each patient Maintenance — no data

BSA — body surface area. Dosages need to be adjusted to renal function according to summary of product characteristics; CMV — cytomegalowirus
* Valgancyclovir dose for children and adolescents should be calculated in accordance with instructions included in summary of drug characteristics. Maximum daily dose in children and adolescents is 1 × 900 mg/day.
** Cidofovir should be given with probenecid.
*** Maribavir is not registered in European Union; in USA it is registered for patients ≥12 years and ≥ 35 kg

Antiviral drug resistance

The definition of CMV drug resistance includes the occurrence of a viral genetic alteration that affects *in vitro* susceptibility and/or clinical response, typically involving genes implicated in antiviral drug metabolism [15].

Some mutations in CMV DNA confer a known level of drug resistance. The most frequent tested mutations are summarized in Table IV [15]. The type of mutation related to a specific resistance can be found in the open-access, international database for resistance and polymorphisms of viral strains [74].

Recommendations for immunotherapy in CMV infection and CMV disease

In patients with post-transplant refractory CMV infection and CMV disease, adoptive T-cell therapy can be considered (BII) [3, 75–85].

Recommendations for monitoring and management of CMV infection and disease after autologous HCT

In patients after autologous hematopoietic stem cell transplantation, routine screening and pre-emptive therapy is not recommended (DII). However, patients at high risk (*i.e.* with autoimmune disease with CD34 selection who are receiving anti-thymocyte globulin) might benefit from monitoring and the use of pre-emptive anti-CMV therapy (CII) [86–88].

Recommendations for other pediatric patients with hematological malignancies

Routine anti-CMV prophylaxis and routine screening for CMV reactivation is not recommended (DIII) [3]. An individual patient might benefit from anti-CMV pre-emptive therapy (BIII).

Table IV. Most frequent CMV mutations and observed resistance to antiviral drugs [15]

Gene	Aminoacids substitution	Comment
UL54	E756 K, A809 V	Resistance to foscarnet
UL54	N408 K, A987G	Resistance to cidofovir
UL56	C325Y/F/W/R, V236M	Resistance to letermovir
UL97	T409M, H411Y	Resistance to maribavir
UL97	F342Y, C4800F	Cross resistance to maribavir and gancyclovir
UL97	M460 V/I, H520Q, C592G, A594 V, L595S, C603W	Resistance to gancyclovir

Epstein-Barr virus

Epstein-Barr virus (EBV) is human herpesvirus type 4 (HHV-4), of the gamma-herpesvirus subfamily belonging to the DNA viruses. It is one of the most common viruses in humans, being an agent of a global infection, with overall prevalence of 85% [89–91]. Most primary infections occur in young children or adolescents. Typically for herpesviruses, pathogenetically EBV presents in the form of primary (acute) or latent infection. The latter can be activated and present as EBV-DNA-emia (also referred to as reactivation or recurrent or secondary infection) which occurs mainly in immunocompromised patients, especially transplant recipients. Nevertheless, in most cases both primary infection and reactivation are subclinical, and usually require no therapy [6].

Clinical symptoms

Syndromes caused by primary EBV infection include infectious mononucleosis, chronic active EBV infection, and X-linked lymphoproliferative disease [6]. The EBV virus does not pose a significant threat to patients undergoing oncological treatment. In HCT patients, EBV can reactivate and cause life-threatening complications *i.e.* post-transplant lymphoproliferative disorder (PTLD), or end-organ diseases such as encephalomyelitis, pneumonia, hepatitis, and rarely hemophagocytic syndromes.

Definitions

EBV-PTLD is a heterogenous group of EBV diseases with neoplastic lymphoproliferation, developing after transplantation and caused by iatrogenic suppression of T-cell function [6]. There are two levels of diagnosis of PTLD: probable and proven, differentiated by performing a biopsy of involved tissue/organ and its confirmation by histopathology [6].

Probable EBV disease is diagnosed in cases of clinical symptoms and/or signs of significant lymphadenopathy, hepatosplenomegaly or other organ manifestations, with the presence of significant EBV-DNA-emia but without biopsy from the affected organ, and in the absence of other documented causes.

Proven EBV disease is diagnosed in the presence of symptoms and/or signs from the involved organ and the detection of EBV-DNA/RNA, virions or EBV-encoded proteins (*e.g.* EBER, EBV-encoded RNA) in a tissue specimen obtained via biopsy or another invasive procedure from this organ [4].

Risk factors

The most frequently reported risk factors contributing to the development of post-transplant EBV infection and EBV-driven diseases include: donor EBV-IgG-seropositivity; the use of T-cell depletion (TCD), especially *in vivo* TCD with ATG (anti-thymocyte globulin); reduced-intensity conditioning; an unrelated donor or mismatched family transplants; and acute and/or chronic graft-versus-host disease [92].

Classification

EBV-PTLDs present a wide heterogeneous spectrum of histologically-defined lymphoproliferative disorders [93]. The 2016 World Health Organization (WHO) classification of lymphomas included six morphological types of PTLDs: infectious mononucleosis, plasmacytic hyperplasia, florid follicular hyperplasia, monomorphic (B-cell or T-/NK-cell types), polymorphic, as well as classical Hodgkin's lymphoma [93, 94]. But a major change in WHO classification was made in 2022. PTLDs are no longer listed in the classification of lymphoid malignancies [95]. This approach applies also in the International Consensus Classification of Mature Lymphoid Neoplasms [96]. Currently, these pathologies are defined broadly as immunodeficiency-associated lymphoproliferative disorders [95] or as lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation [96].

Diagnostics

Before transplant

All allo-HCT patients and donors should be tested for anti-EBV IgG antibodies before HCT (AII). Currently, there is no justification for testing of EBV-DNA before HCT or during standard chemotherapy (AII).

After transplant

After allo-HCT, regular weekly monitoring of EBV viral load by PCR is recommended. This monitoring should start soon after transplantation and no later than at neutrophil engraftment, since about 6% of EBV-PTLDs can develop during the first month after transplantation. The monitoring

should be continued until the end of immunosuppressive treatment, and at least until day +120 (AII). Since EBV-PTLD by definition should be regarded as a secondary cancer, diagnostics of EBV-PTLD requires: EBV-DNA-emia testing, imaging preferentially with PET-CT/MRI or CT/MRI, biopsy of the affected organ, and histological testing for the presence of EBV markers, preferably EBER (EBV-encoded RNA) (AII).

Prophylaxis

Non-specific prevention

Since EBV-PTLD after HCT is usually of donor origin and EBV can be transmitted with donor graft material, the risk of EBV-PTLD is higher when the donor is seropositive (BII). Additionally, donor EBV-seropositivity is a risk factor for developing chronic GVHD (and, to a lesser extent, acute GVHD) [90, 91]. Therefore, selecting an EBV-negative donor might be beneficial. EBV serological incompatibility in cases of recipient EBV-IgG-seropositivity should no longer be regarded as beneficial, as it increases the risk of EBV-PTLD (as it is of donor origin!), and increases the risk of cGHVD and aGVHD. There is also evidence that, unlike CMV, in cases of donor EBV-IgG-seropositivity, no protective EBV-specific cytotoxic T-lymphocytes (CTLs) are transferred with the graft [97].

Specific prophylaxis

Since EBV virions in latent form stay and replicate in B-lymphocytes, anti-CD20 antibodies are an option against any EBV-driven post-transplant complications, including preventing EBV reactivation in high-risk patients (BII). A single dose of 150–200 mg/m^2 is used either before or after transplantation (day +5) [98]. New prophylactic options are cytotoxic lymphocytes with anti-EBV specificity (EBV-CTL; EBV-VST, viral specific T-lymphocytes) or multi-specific (multi-VST), either derived from a donor or 'off-the-shelf'. Tabelecleucel (Tab-cel; Ebvallo, Atara), is an 'off-the-shelf' third-party-donor, monospecific EBV-CTL, approved by the EMA for treatment of resistant/refractory EBV-PTLD [99–101]. However, due to its high cost, it is unlikely that this product will be used, or even tested, for anti-EBV prophylaxis. On the other hand, the multi-specific agent posoleucel (activity against six DNA viruses: ADV, BKV, CMV, EBV, HHV-6, and JCV) (CII) has shown high activity both in prophylaxis (EBMT-2023, abstract OS08-03) and therapy [102], but currently this product is not available for any indication, and all clinical trials with this product have been completed or discontinued.

Available antiviral drugs have no activity against the latent form of EBV (AII). Other approaches, such as immunoglobulins or interferons, are also not effective against EBV.

Treatment

In a non-transplant setting, EBV reactivations are subclinical and do not require any treatment. Patients after allo-HCT, and exceptionally patients with other immune deficiencies, require treatment. There are two therapeutic options against EBV after allo-HCT: pre-emptive treatment and targeted treatment.

Preemptive therapy can be defined as the administration of a drug or cellular therapy to a patient with EBV viremia (EBV-DNA-emia) in order to prevent the development of EBV disease.

Targeted treatment of a clinically confirmed EBV disease (such as EBV-PTLD) means therapeutic interventions used in patients with probable or proven EBV disease.

EBV-related complications usually denote involvement of the lymphoid tissue, anatomically localized throughout the whole body. Thus, both EBV-DNA-emia and EBV-PTLD have to be regarded as a disseminated disease at diagnosis, and the treatment modalities must include systemic intervention. The therapeutic approaches which can be applied in the prevention, pre-emptive and targeted treatment of EBV-related complications include: administration of anti-CD20 antibodies, rituximab, reduction of immunosuppression (RIS), use of EBV-CTLs or donor lymphocyte infusion (DLI), and rarely chemotherapy, while other modalities have nowadays only a historical value.

Pre-emptive therapy is recommended for patients with a clinically significant EBV viral load (AII). The viral load limit must be determined at the transplant center Most transplant centers use pre-emptive therapy with EBV-DNA-emia values in the range of 10^3–10^4 IU/mL (or: copies/mL) [4, 103, 104]. Anti-CD20 antibodies (AII) are preferentially used in first-line pre-emptive therapy. Reduction of immunosuppression (RIS) is always recommended if possible (AII), assuming that RIS is defined as a reduction of drug dose by ≥20%. Currently, effectiveness of first-line pre-emptive therapy is in the range of 90–95%. Second-line pre-emptive therapy includes CTL/VST or DLI (CII). On the other hand, due to a lack of effectiveness, therapy with antiviral drugs, IGIV, interferon (AII) is not recommended.

In clinically diagnosed EBV-PTLD, first-line therapy uses anti-CD20 antibodies and RIS if possible (AII). With these two therapeutic modalities, the current success rate of first-line therapy is c.70% [4, 103, 105, 106]. In cases of refractory/resistant or relapsing EBV-PTLD, second-line therapy is recommended, which is based on the use of CTL/VST (BII) or chemotherapy (CII). However, chemotherapy is a limited option in HCT patients due to high toxicity (CIII). DLI used to be recommended as an additional option in second-line therapy, but these days the role of DLI in treatment of EBV-PTLD is marginal, mainly due to limited efficacy and the recent observation of a lack of presence of EBV-specific cytotoxic T-lymphocytes (CTLs) transferred in the graft from donor [97].

The role of EBV-specific CTLs is currently growing, due to better access of transplant centers to the production of EBV-CTL, both donor-derived and 'off-the-shelf' third-party

Table V. Summary of therapeutic options for prophylaxis and therapy against EBV-DNA-emia and EBV-PTLD

Therapeutic option	Prophylaxis of DNA-emia	Preemptive therapy	Therapy of EBV-PTLD		
			First line	Second line	CNS involvement
Rituximab	CII	AII	AII	AII	BIII
RIS		AII	AII		
Rituximab + RIS		AII	AII	AII	
EBV-CTL	CII	CII	CII	BII	CIII
DLI				CIII	
Chemotherapy ± rituximab				CII	BII
Radiotherapy					CIII
Antivirals	DII	DII	DII	DIII	DII
IVIG	DIII			DIII	
Surgery				DIII	

DLI — donor lymphocyte infusion; EBV-CTL — cytotoxic T-lymphocytes; IVIG — intravenous immunoglobulins; RIS — reduction of immunosuppression

donor. As mentioned before, tabelecleucel (Tab-cel, Ebvallo) is licensed by the EMA for the treatment of resistant EBV-PTLD. A US FDA license for Ebvallo in this indication is expected in 2025. A summary of the therapeutic options for prophylaxis and therapy against EBV-DNA-emia and EBV-PTLD is presented in Table V.

Herpes simplex virus

Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), after primary infection, establish latency in the dorsal root ganglia of sensory neurons and exhibit the potential of reactivation by various external stimuli such as immune suppression [107]. HSV-1/2 usually causes localized mucocutaneous disease in the orofacial region (commonly) or genital region (less frequently). In immunocompromised patients, it most commonly manifests as stomatitis and oesophagitis, while other less common manifestations include meningitis, encephalitis, hepatitis, pneumonia and bone marrow suppression [108–111]. Most HSV reactivations occur during the first month after HCT.

Diagnosis

Hematopoietic cell transplantation candidates should be tested for serum anti-HSV IgG before transplantation (BII) [6]. However, in Polish pediatric transplant centers, testing for IgG seropositivity is very rarely carried out. Serological testing is not helpful in confirming the diagnosis of HSV reactivation (DIII) [6]. Mucocutaneous HSV disease is diagnosed based on clinical manifestation and can be confirmed by PCR in a sample obtained from the lesion (BIII). In cases of meningitis/encephalitis, the diagnosis should be based on PCR in CSF (AII) [6, 112]. Routine monitoring of HSV after HCT is not recommended (DIII) [6, 112, 113].

Prophylaxis

Oral prophylaxis is recommended and acyclovir is the drug of choice. Most experience in this area comes from studies done before 2000, supplemented by expert opinion from ECIL [6] and EBMT [112]. Prophylaxis with oral/intravenous acyclovir (5 mg/kg every 12 h, 3 × 200 mg to 2 × 800 mg daily *p.o.* or 250 mg/m^2 *i.v.*) is recommended for seropositive patients undergoing HCT for 3–5 weeks after HCT (AI) [6, 112, 114]. Allo-HCT recipients developing GVHD, patients undergoing immunosuppressive treatment, and children treated for acute leukemia require prolonged prophylaxis [6, 112] (BII). Although primary HSV infections in seronegative patients undergoing HCT are uncommon, primary prophylaxis with acyclovir may be considered (CIII) [6, 112]. Valacyclovir (2 × 500 mg daily *p.o.*) can be used for HSV prophylaxis in children over 12 (BIII) [6, 112]. For HSV-seropositive auto-HCT recipients with a significant risk of developing HSV infection, antiviral prophylaxis can be applied according to the aforementioned strategy (BII) [115, 116].

Treatment

The treatment of choice for severe mucocutaneous disease or visceral disease is intravenous acyclovir (250 mg/m^2 or 5 mg/kg every 8 h for 7–10 days) [6, 112] (AI). Less serious cases of mucocutaneous HSV disease can be treated with oral acyclovir (5 × 5 mg/kg/day *p.o.* or 5 × 200 mg to 5 × 400 mg) (AI) or valacyclovir in children over the age of 12 (2 × 500 mg) (BIII) [6, 112].

Pneumonia, meningitis and encephalitis should be treated with intravenous acyclovir (500 mg/m^2 or 10 mg/kg every 8 h for 14–21 days) (CIII) [6, 112]. In cases of resistance to acyclovir, second-line treatment comprises intravenous foscarnet (60 mg/kg every 12 h or 40 mg/kg every 8 h for 7–21 days until complete healing) (BIII) or intravenous cidofovir (5 mg/kg once a week for two weeks, then once every two weeks, with simultaneous probenecid and hydration required) (BIII) [6, 115, 117]. In cases of persistent mucocutaneous HSV disease, the following topical agents may be used: cidofovir 1% cream, cidofovir 3% oral rinse, and foscarnet 2.5% cream (CIII) [118].

Acyclovir dosing in HSV/VZV prophylaxis and treatment is summarized in Table VI.

Varicella-zoster virus

Clinical manifestations

Varicella-zoster virus (VZV) in the case of primary infection causes varicella, a childhood disease with characteristic

Table VI. Acyclovir dosing in HSV/VZV prophylaxis and treatment in children

	Prophylaxis	Treatment
HSV	2 × 5 mg/kg/day *i.v.* or 250 mg/m^2 *i.v., p.o.*	5 × 5 mg/kg/day *p.o.* (less serious manifestations) 3 × 5 mg/kg/day) *i.v.* or 250 mg/m^2 *i.v.* (mucocutaneous/visceral manifestation) 3 × 10 mg/kg/day *i.v.* or 3 × 500 mg/m^2 *i.v.* (HSV pneumonia/meningitis)
VZV	IgG(+) patients: 2 × 20 mg/kg/day *p.o.* IgG(–) patients after exposure 2 × 20 mg/kg/day *p.o.*	Shingles: 4 × 20 mg/kg/day (max. 4 × 800 mg/day) *p.o.* Chickenpox: 3 × 500 mg/m^2/day *i.v.*

CMV — cytomegalovirus; HSV — herpes simplex virus; VZV — varicella zoster virus

vesicular rash and pruritus. Varicella recovery results in VZV latency in the nerve ganglia. Reactivation of the VZV causes shingles/herpes zoster (HZ) vesicular eruptions involving one or more dermatomes accompanied by pain and hyperesthesia [115, 119, 120]. Seronegative patients undergoing chemotherapy or receiving hematopoietic cell transplantation are at risk of developing severe, or even fatal, varicella as a result of contact with someone with a VZV infection. In this group of patients, in addition to generalized pruritus, alveolar rash and high fever, VZV infection may manifest as hepatitis, pneumonia or encephalitis [115, 119, 120]. Contrary to immunocompetent patients, in children undergoing oncological treatment or after HCT, VZV/HZ reactivation usually is more severe, involves more dermatomes, and can involve the liver, stomach, peritoneum, an/or intestines, or may spread to the meninges or brain in cases of ocular or auricular shingles [115, 119, 120].

Diagnosis

Patients should be tested for VZV antibodies before HCT (AIII). PCR VZV-DNA testing is the recommended method to confirm infection or reactivation of VZV. PCR VZV-DNA can be assessed in peripheral blood, cerebrospinal fluid, as well as swabs from smallpox or shingles vesicles. Quantitative assessment of VZV-DNA allows for the monitoring of responses to treatment in cases of the involvement of internal organs when not accompanied by a characteristic rash [6, 115].

Prophylaxis

Patients with leukemia and candidates for HCT should be instructed about the risks and pathways of infection or reactivation of VZV (AII). Seronegative patients should avoid contact with patients with chickenpox or shingles (AII). It is also recommended to avoid contact with people who have been vaccinated against smallpox (BIII). VZV seropositive patients should receive prophylaxis with oral acyclovir or valacyclovir at least up to 12 months after HCT (AII) or until immunosuppression is discontinued (BII). Seronegative patients who are exposed to VZV should receive post-exposure prophylaxis. Immunocompromised patients should receive VZIG (varicella zoster immune globulin) as soon as possible, but not later than 96 hours after household or close contact. If VZIG is not available, patients should receive intravenous immune globulin and antiviral therapy, *i.e.* acyclovir or valacyclovir, starting within 3–21 days after exposure (AIII); antiviral therapy at therapeutic doses should be continued up to 21 days after exposure. Post-exposure prophylaxis for VZV seropositive patients is optional (CIII) [6, 115, 121–123].

Cocoon strategy vaccinations are recommended, *i.e.* involving seronegative family members and/or people who will be in contact with the patient during the peri-transplant period (BIII). Vaccinations should be done >4 weeks before the start of conditioning (BIII).

Seronegative patients could be vaccinated against VZV with a live attenuated vaccine (Varivax, Varilix) at least 24 months after allo-HCT in the absence of GVHD and/or immunosuppression (AIII) [6, 124, 125]. A recombinant vaccine against shingles is available, which has been used in studies in adult patients after allo-HCT, but in Poland it is not registered for children.

All patients with chickenpox or disseminated shingles require contact isolation until the lesions have dried (BIII) [6, 124–126].

Treatment

The first line of treatment for chickenpox in patients with acute leukemia or HCT recipients is intravenous acyclovir 3 × 500 mg/m^2/day (AI). Involvement of internal organs (pneumonia, hepatitis or encephalitis) in the course of VZV infection should be treated like chickenpox, *i.e.* with intravenous acyclovir 500 mg/m^2 every eight hours (AIII). For localized shingles, oral therapy with acyclovir (20 mg/kg four times a day) can be used; alternatively, valacyclovir or famcyclovir can be applied (CII). Intravenous or oral treatment should be carried out for at least seven days, and continued for two days after all follicular lesions have dried (AI). Follicular eruptions that have occurred after smallpox vaccination should be treated similarly (BIII) [6, 115, 119, 120].

For VZV infections refractory to acyclovir treatment, foscarnet (60 mg/kg every 12 hours) or cidofovir (5 mg/kg weekly every two weeks in combination with probenecid and hydration) should be used (AIII) [6, 127, 128]. Acyclovir dosing in VZV prophylaxis and chickenpox/shingles in children is summarized in Table VI.

Human herpesvirus 6

Human herpesvirus 6 (HHV-6) has been classified into two subtypes: HHV-6A and HHV-6B [5, 129]. HHV-6A is so far not known to cause any specific infection, although it has been suggested that it may play a role in multiple sclerosis, especially at the onset of the disease. HHV-6B is a causative agent of exanthema subitum and affects 90% of infants by the age of 2 years [5, 129–132]. Among patients after allo-HCT, HHV-6 can lead to bone marrow suppression, encephalitis (especially HHV-6B), pneumonia, acute GVHD, fever and rash [133, 134]. The prevalence of chromosomal integration of HHV-6 (CI-HHV-6) in the general population is approximately 1% [113]. Reactivation of HHV-6 infection in pediatric cancer patients during chemotherapy is infrequent, but can lead to severe complications as described above [113].

Diagnostics

There is no recommendation for recipients and donors to be tested for HHV-6 before allo-HCT. Diagnosis of HHV-6 reactivation/infection is based on analysis of blood or bone marrow by quantitative PCR (AII), while the diagnosis of HHV-6 encephalitis is based on clinical symptoms, MRI scan and the presence of HHV-6 DNA in CSF (BII). Chromosomal integration of HHV-6 can complicate diagnostics, as these patients have markedly elevated HHV-6 DNA levels due to the presence of HHV-6 in every nucleated cell. CI-HHV-6 should be excluded at the moment of HHV-6 reactivation diagnosis [5, 129]. There are several options to exclude CI-HHV-6. The best way is to test hair follicles or nails, since HHV-6 DNA is present in hair follicles and nails exclusively in persons with CI-HHV-6 [5].

Prophylaxis

Routine screening of HHV-6 DNA in blood after allo-HCT is not recommended (DII). Anti-HHV-6 prophylactic or pre-emptive therapy is not recommended for the prevention of HHV-6 reactivation or encephalitis after allo-HCT (DII). Routine prospective testing of HHV-6 DNA may be considered after cord blood allo-HCT for a short time (2–6 weeks) following transplantation (CIII) [5, 135].

Treatment

Most HHV-6 reactivations are asymptomatic or subclinical and do not need treatment. Intravenous gancyclovir or foscarnet are recommended for the treatment of HHV-6 encephalitis or other end-organ diseases (AII). The recommended dose for gancyclovir is 2 × 5 mg/kg/day *i.v.*, and for foscarnet 180 mg/day *i.v.* (3 × 60 mg or 2 × 90 mg/kg) (AII). The treatment should be continued for at least three weeks and until viral clearance (CIII). Reduction of IST is recommended if possible (BIII). Combination therapy with gancyclovir and foscarnet may be considered (CIII). Viral specific donor T lymphocytes (VST) may be considered in refractory disease (CIII). Several options have been tested in an autologous or allogeneic T-cell setting, mainly as a polyvalent option [102]. Nevertheless, experience with and availability of anti-HHV-6-VST is limited.

Human herpesvirus 7

Primary human herpesvirus 7 (HHV-7) infection causes exanthema subitum and affects most children by the age of 5. Reactivation of HHV-7 is relatively infrequently observed in HCT recipients, including pediatric patients, and clinical manifestations like encephalitis or myelitis directly due to HHV-7 seem very rare in these patients [136].

Diagnostics

There is no recommendation for recipients and donors to be tested towards HHV-7 before allo-HCT. Diagnosis of HHV-7 reactivation/infection is based on analysis by quantitative PCR (C III) [112].

Prophylaxis

Routine screening of HHV-7 DNA in blood after allo-HCT is not recommended (DIII). Anti-HHV-7 prophylactic or pre-emptive therapy is not recommended for the prevention of HHV-7 reactivation or disease after allo-HCT (DIII) [112].

Treatment

Infection by HHV-7 does not require specific treatment (D III) [112].

Human herpesvirus 8

Human herpesvirus 8 (HHV-8) can cause Kaposi's sarcoma (KS), primary effusion lymphoma and Castleman's Disease — the last of these having not been reported after HCT. HHV-8 is very rare after HCT, and can manifest as fever, skin involvement (mainly in adults), bone marrow aplasia, plasmocytosis, or visceral dissemination (mainly in children) [113]. Clinical syndromes with hepatitis with or without hemophagocytic syndromes have been reported [137]. An EBMT study reported the incidence of Kaposi's sarcoma to be 0.05% for autologous and 0.17% for allogeneic HCT [138].

Diagnostics

There is no recommendation for serological testing of recipients and donors for HHV-8 before allo-HCT (D III). Although the diagnosis of KS is usually clinically or histopathologically defined, detection of HHV8-DNA in blood may assist with diagnosis where the site of malignancy is not accessible for biopsy (BIII) [139]. For prompt diagnosis, risk factors and local seroprevalence should be kept in mind (BIII) [115].

Prophylaxis

There is no data to guide monitoring or preemptive antiviral treatment for post-transplant HHV8-associated disease (DIII) [112, 115].

Treatment

Preliminary data indicates that reduction of IS may lead to a regression of KS lesions (C III) [140]. In skin involvement, surgical excision or electrochemotherapy are preferred (A III) [112]. In disseminated disease, interferon-alpha or chemotherapy are recommended. (A III) [112]. Antivirals should not be routinely used to treat HHV8-related disease (D III) [141].

Conclusions

Herpesviruses are one of the major pathogens in patients with hematological malignancies, especially after allogeneic HCT. New methods of diagnosis and treatment pose challenges in determining optimal management strategies for antiviral prophylaxis and treatment. Recently, new drugs such as letermovir and maribavir or new therapies such as viral specific T-cells have been shown to be promising clinical players in this setting.

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Conflict of interest

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Data availability statement

Not applicable.

Authors' contributions

KC, JS: design of study; KC, JS, AS-S, AP, MD: writing manuscript; All authors: analysis of recommendations, final approval. Authors responsible for particular sections: Introduction, Methods, Conclusions: KC, JS; CMV — KC; EBV — JS; HSV — MD; VZV — AP; HHV-6, HHV-7, HHV-8 — AS-S.

Supplementary material

None.

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