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ABC of viral infections in hematology: focus on herpesviruses

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Abstract

Viruses are a form of life that possess genes but do not have a cellular structure. Viruses do not have their own metabolism, and they require a host cell to make new products; therefore, they cannot naturally reproduce outside a host cell. The objective of this paper is to present the basic practical clinical roles of viruses in patients with hematological diseases including malignancies and non-malignancies, as well as those undergoing hematopoietic cell transplantation (HCT), with the focus on herpesviruses causing latent infections in severely immunocompromised patients. From the hematologist point of view, viruses can play a major role in four conditions: causing infections; causing lymphoproliferations and/or malignancies; causing (pan)cytopenia; and used as vectors in treatment (e.g., gene therapy, CAR-T cells). Taking into account the role of viruses in hematology, infection is the most frequent condition. Among DNA viruses, the highest morbidity potential for human is expressed by Herpesviridiae (herpesviruses), Adenoviridae (adenovirus; ADV), Polyomavirus (BKV, JCV), and Bocavirus. RNA viruses can play a role in pathogenesis of different clinical conditions and diseases: lymphoproliferative disorders and malignancy, possibly causing NHL, AML, MDS, and others (HCV, HIV, and others); pancytopenia and aplastic anemia (HIV, HCV, Dengue virus); respiratory infections (community-acquired respiratory virus infections; CARV) caused by Orthomyxoviruses (e.g. influenza A/B), Paramyxoviruses (e.g. human parainfluenza virus PIV-1, -2, -3, and -4; respiratory syncytial virus RSV-A and -B), picornaviruses (e.g., human rhinovirus), coronaviruses (e.g., human coronavirus), Pneumoviridiae (e.g., human metapneumovirus), and potentially other viruses.

Keywords:
herpesviruses, CMV, EBV, HHV-6, VZV

Introduction

Viruses are a form of life that possess genes but do not have a cellular structure. Viruses do not have their own metabolism, and they require a host cell to make new products; therefore, they cannot naturally reproduce outside a host cell [1]. The complete set of viruses in an organism or habitat is called the virome; for example, all human viruses constitute the human virome [2]. Although there are millions of different types of viruses, only about 5,000 types have been described in detail [3]. A virus has either a DNA or an RNA genome and is called a DNA virus or an RNA virus, respectively.

The objective of this paper is to present the basic practical clinical roles of viruses in patients with hematological diseases including malignancies and non-malignancies, as well as those undergoing hematopoietic cell transplantation (HCT), with the focus on herpesviruses causing latent infections in severely immunocompromised patients.

Classification

The current classification of viruses was developed by The International Committee on Taxonomy of Viruses (ICTV). As of June 2019, 14 orders, 143 families, 64 subfamilies, 846 genera and almost 5000 species of viruses have been defined by the ICTV. The orders are the Caudovirales, Herpesvirales, Ligamenvirales, Mononegavirales, Nidovirales, Ortervirales, Picornavirales, Bunyavirales, Tymovirales, Muvirales, Serpentovirales, Jingchuvirales, Goujianvirales, and Articulavirales (Virus Metadata Resource; https://talk.ictvonline.org/taxonomy/vmr/).

Baltimore classification of viruses is based on the DNA or RNA of virus and method of mRNA synthesis [4]. Viral genomes may be RNA or DNA, single-stranded (ss) or double-stranded (ds), and may or may not use reverse transcriptase (RT). Additionally, ssRNA viruses may be either sense (+) or antisense (−). The vast majority of viruses have RNA genomes. Baltimore classification divides viruses into seven groups (Tab. I).

Role of viruses in hematology

From the hematologist point of view, viruses can play a major role in four conditions: causing infections; causing lymphoproliferations and/or malignancies; causing (pan)cytopenia; and used as vectors in treatment (e.g., gene therapy, CAR-T cells) (Tab. II).

Taking into the role of viruses in hematology, infection is the most frequent condition. Among DNA viruses, the highest morbidity potential for human is expressed by Herpesviridiae (herpes viruses), Adenoviridae (adenovirus; ADV), Polyomavirus (BKV, JCV), and Bocavirus.

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RNA viruses can play a role in pathogenesis of different clinical conditions and diseases: lymphoproliferative disorders and malignancy, possibly causing NHL, AML, MDS, and others (HCV, HIV, and potentially Dengue virus, Zika virus, Chickungunya virus); pancytopenia and aplastic anemia (HIV, HCV, Dengue virus); respiratory infections (community-acquired respiratory virus infections; CARV) caused by Orthomyxoviruses (e.g., influenza A/B), Paramyxoviruses (e.g., human parainfluenza virus PIV-1, -2, -3, and -4; respiratory syncytial virus RSV-A and -B), Picornaviruses (e.g., human rhinovirus), coronaviruses (e.g., human coronavirus), Pneumoviridiae (e.g., human metapneumovirus), and potentially other viruses.

Diagnostics of viral infections in hematological patients

Laboratory test for viral infections with focus on latent and chronic infections should be performed in many hematological conditions, especially at diagnosis of the disease, and before HCT (both in recipient and donor). Additionally, after HCT monitoring for CMV and EBV, reactivation is mandatory in allo-HCT setting, and for several other viruses depending on clinical signs and symptoms (Tab. III).

Viral infections

Viral infections are a major issue for hematopoietic cell transplant (HCT) recipients. The most important viral pathogens in this group of patients include herpes simplex viruses (HSV-1 and HSV-2), varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr Virus (EBV), human herpes 6 virus (HHV6), adenovirus (ADV), BK virus (BKV), influenza, parainfluenza, respiratory syncytial virus (RSV), rhinovirus, and norovirus. Other pathogenic viruses include enteroviruses, HIV, hepatitis, JCV, and parvovirus (PVB19).

Reactivation of latent infections with herpes viruses may lead to various disease manifestations, regardless of its primary acquisition after the transplant. Unlike in the general immunocompetent population, with typical clinical manifestations of infection ranging from asymptomatic to mild or moderate symptoms, HCT recipients may frequently develop much more severe disease.

It is essential to identify patients at risk for reactivation of latent viruses, as active infection and diseases can often be prevented with prophylaxis and preemptive monitoring during the most critical time periods.

Herpes viruses

Herpesviridae create a large family of double-stranded DNA viruses with specific and unique biologic features, enabling them to establish latency program after primary infection in human prior to reactivation later in life. With respect to taxonomy, there are three subfamilies: alpha-, beta-, and gamma-herpes-viridiae, which include nine known human herpesviruses (Tab. IV).

In the most severely immunocompromised patients, which comprise mainly recipients of allo-HCT from unrelated or mismatched donor, four herpesviruses play a major role in chronic latent and relapsing infections including CMV, EBV, HHV6B, and VZV. So far, no pathogenicity was shown for HHV-6A virus. These four viruses are described and discussed in this article. Basic characteristics of these four herpesviruses are shown in table V [5–8].

Herpes simplex virus. HSV-1 and HSV-2 infection is usually associated with mucocutaneous disease in the orofacial region (85%–90%), and rarely in the esophageal and genital area. Rare

Table I. Baltimore classification of viruses

Group	Category	Examples
I	dsDNA viruses	Adenoviruses, Herpesviruses, Poxviruses
II	ssDNA viruses (+ strand or „sense") DNA	Parvoviruses
III	dsRNA viruses	Reoviruses
IV	(+)ssRNA viruses (+ strand or sense) RNA	Picornaviruses, Togaviruses
V	(–)ssRNA viruses (– strand or antisense) RNA	Orthomyxoviruses, Rhabdoviruses
VI	ssRNA-RT viruses (+ strand or sense) RNA with DNA intermediate in life-cycle	Retroviruses
VII	dsDNA-RT viruses DNA with RNA intermediate in life-cycle	Hepadnaviruses

Table II. Role of viruses in hematology

Role	Examples
Causing infections	Episodic infections (CARV) Latent infections (herpesviruses, ADV, BKV, JCV) Hepatotropic infections (HBV, HCV, HEV)
Causing lymphoproliferations and/or malignancy	EBV, HTLV (HIV, HCV)
Causing pancytopenias	PVB19, HAV, HCV, HIV, DENV
Used in treatment	Retroviruses, Lentiviruses (vectors for CAR-T cells, gene therapy)

Abbreviations in text.

Table III. Mandatory screening tests for viral infections in hematology

Clinical situation	Viral test
Malignancy at diagnosis	CMV, EBV, HIV, HBV, HCV (serology)
Before HCT	CMV, EBV, HIV, HBV, HCV, (HSV, VZV) (serology)
Donor HSC	CMV, EBV, HIV, HBV, HCV (serology)
After allo-HCT	CMV, EBV (NAT)
Thrombocytopenia	CMV, EBV, HIV
Pancytopenia	CMV, EBV, HIV, HAV, HBV, HCV, PVB19
Leukocytosis	EBV, CMV, HCV
Respiratory infection	CARV, ADV, CMV
Hemorrhagic cystitis	BKV, ADV, CMV
Encephalitis	HHV6, CMV, EBV, JCV, VZV, HSV
Hepatitis	HAV, HBV, HCV, HDV, HEV and other

NAT (nucleic acid test); other abbreviations in text.

manifestations are meningitis, encephalitis, pneumonia, and hepatitis. Mucocutaneous HSV disease is diagnosed clinically and can be confirmed by PCR. HSV meningitis and encephalitis should be confirmed by PCR in cerebrospinal fluid. Antiviral drug prophylaxis is not recommended in HSV-seronegative patients after HCT (except anti-VZV prophylaxis). HSV-seropositive patients should receive antiviral drug prophylaxis after allo-HCT. Intravenous acyclovir 250 mg/m^2 or 5 mg/kg every 12 h, oral acyclovir 3 x 200 to 2 x 800 mg/day, oral valaciclovir 2 x 500 mg/day, or famciclovir 2 x 500 mg/day can be used, for a period of at least 4 weeks after HCT in VZV-seronegative patients. Intravenous acyclovir remains the therapy of choice for severe mucocutaneous or visceral HSV disease. 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. Oral acyclovir, from 5 x 200 to 5 x 400 mg/day, valaciclovir 2 x 500 mg/day, or famciclovir 2 x 500 mg/day for 10 days are considered as alternatives for less serious manifestations of HSV disease. For HSV pneumonia or HSV meningitis and encephalitis, i.v. acyclovir 500 mg/m^2 or 10 mg/kg every 8 h for at least 14–21 days is recommended. HSV resistance occurs in approximately 5%–15% of patients and foscarnet or cidofovir is second-line therapy [5].

HHV-7 primary infection in young children (<5y) causes *exanthema subitum (roseola)* and rarely status epilepticus with fever. Reactivation of HHV-7 occurs in about 10% of patients after allo-HCT. Clinically, overt HHV-7 detection after HCT is rare and might be associated with CNS disease (encephalitis or myelitis). Diagnosis of HHV-7 is made by qPCR. Usually, infection with HHV-7 does not require specific treatment [6].

HHV-8 (KSHV, Kaposi's sarcoma-associated herpesvirus) is the cause of Kaposi's sarcoma (KS), as well as primary effusion lymphoma and Castleman's disease. KS is extremely rare after HCT with skin involvement, fever, and marrow aplasia with plasmocytosis. Pediatric cases might have visceral involvement. Diagnosis of HHV-8 is made by qPCR. KS can be confirmed histopathologically as malignant tumor. In skin manifestation, surgical excision or electrochemotherapy is the preferable approach. For other manifestations, possible options include the following: interferon-alpha, chemotherapy, and radiotherapy [9,10]. The use of antiviral treatment is not recommended.

Table IV. Family of Herpesviridiae

SUBFAMILY	Species	Viruses
Alpha-herpes-viridiae	Simplex-virus	HHV-1=HSV-1, HHV-2=HSV-2
	Varicello-virus	HHV-3=VZV
Beta-herpes-viridiae	Cytomegalo-virus	HHV-5=CMV
	Muromagalo-virus	
	Roselo-virus	HHV-6A/HHV-6B, HHV-7
Gamma-herpes-viridiae	Lympho-crypto-virus	HHV-4=EBV, HHV-8=KSHV
	Rhadino-virus	

Abbreviations in text.

Herpes viruses seroprevalence: increasing with age

The human herpesviruses, such as CMV, EBV, HHV6, and VZV, are being the agents of a global infection although differences in the

Table V. Basic characteristics of CMV, EBV, HHV6, and VZV infections in HCT setting

Characteristics	CMV	EBV	HHV6	VZV
Taxonomy	HHV-5	HHV-4	HHV-6	HHV-3
Family	Herpesviridae	Herpesviridae	Herpesviridae	Herpesviridae
Subfamily	beta	gamma	beta	alpha
Nucleic acid	ds DNA	ds DNA	ds DNA	ds DNA
Year first identified	1956	1964	1986	1888
Incubation period	3-12 weeks	3-7 weeks	1-2 weeks	2-3 weeks
Seroprevalence in children	30-50%	30-50%	First infection in first two years of life; (CIHHV6: 1%)	67% (age: 1-4y)
Seroprevalence in adults	>70%	>90%	>97% (HHV6 B) (CIHHV6 – 1%)	>98%
Congenital infection	Yes (TORCH)	Yes (rare; asymptomatic)	Congenital (vertical) CIHHV6 (inherited from mother or father)	Yes (TORCH)
Confirmed modes of transmission	With blood and other body fluids (saliva)	With saliva and other body fluids; Kissing disease (saliva)	With saliva and other body fluids	Airborne route or through contact* with contaminated environment
Viral transmission:				
Breastfeeding	Yes	Yes	Yes	No
Organ transplants	Yes	Yes	Yes	No
Blood transfusions	Yes	Yes	Yes	No
Transfer with HSC	Yes	Yes	Yes	No

**EXPOSURE: 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 (acc. to ECIL-2)*

Table VI. Clinical syndromes and symptoms

Clinical symptoms	CMV	EBV	HHV6 A/B	VZV
Asymptomatic	Yes	Yes	Yes None (HHV-6A)	Possible
Mild (general population)	CMV disease (mononucleosis-like)	Mononucleosis	Exanthema subitum (±HHV7)	Varicella Herpes zoster
Severe	Pneumonia, GI infection, hepatitis, BM suppression, retinitis	PTLD*, end-organ diseases, HLH, chronic fatigue syndrome	Encephalitis; CNS dysfunction; pneumonia; BM suppression; hepatitis; IPS	Visceral (encephalitis, pneumonitis, hepatitis); Neuralgia

**PTLD: Heterogeneous group of EBV diseases with neoplastic lymphoproliferation, developing after transplantation and caused by iatrogenic suppression of T-cell function*

Table VII. Incidence of reactivation in patients after HCT

Incidence	CMV	EBV	HHV6	VZV
Reactivation (without prophylaxis)	30%–35%	Median 29% (0.1%–63%)	30%–70%	25%–50%
Symptomatic clinical disease after HCT	1%–2% up to 11% at 1y [8]	3% (1% MFD, up to 11% MMUD/haplo) [7]	0.5% (BM/PB) 8.3%–11.6% (CBT) [14,16]	30%–60% (without prophylaxis) [5]

MFD (matched family donor); MMUD (mismatched unrelated donor); CBT (cord blood transplantation); BM (bone marrow); PB (peripheral blood)

seroprevalence exist between countries: it is the well-documented fact in case of CMV [5–8]. CMV acquisition in a general population is characterized by an age-dependent rise in seropositivity, which correlates most closely with socioeconomic level as well as race, similarly to other herpesviruses [11]. Seroprevalence of CMV varies from about 40%–50% in highly developed countries to over 90% of population in the developing countries, with the rate from about 30% in childhood to over 50% of women of childbearing age and even up to 60%–70% in adults. However, the incidence slightly decreases with the calendar year. Nevertheless, in population of highly developed countries, CMV acquisition still occurs at a rate of 1%–7% per year [8, 9,11–13].

There is an exception in case of HHV-6, as apart from seroprevalence after acquired infection, mainly in early childhood, there is a congenital phenomenon of chromosomally integrated HHV-6 (CIHHV-6), resulting from vertical transmission: inherited from mother or father. It occurs both in HHV-6A or HHV-6B with prevalence about 1% in the general population. In case of CIHHV-6, the virus HHV-6 present in every nucleated cell, and HHV-6 DNA can be easily detected in hair follicles and nails. In most cases, there is one copy of HHV-6 DNA/leukocyte [14,15].

Clinical symptoms: many manifestations

Some of herpesviruses have a potential to play a role in pathogenesis of different diseases with various manifestations. This is well observed in case of EBV and CMV, and it happens also for HHV6 and VZV (Tab. VI).

Also CIHHV-6 can be associated with several diseases. There is a good evidence of association with aGVHD and CMV reactivation [14]. It is probably associated with angina pectoris in general population, and there are known cases of hemophagocytosis with thrombotic microangiopathy in SCID patients, as well as encephalitis post-HCT.

Risk factors and incidence of reactivation

Risk factors of herpes virus recurrence after allo-HCT depend on the following: recipient (virus serology; age), donor (virus serology match; age; sex match; HLA match; type of family/unrelated donor; stem cell source), transplant (type of conditioning: TBI-or chemotherapy-based; T-cell depletion; intensity of myeloablative or reduced intensity conditioning, RIC), immunosuppressive treatment (prophylaxis, occurrence and treatment of acute and/or chronic GVHD; immunosuppressive drugs used in prophylaxis and/or therapy), as well as immune recovery after HCT (speed of immune reconstitution for B cells, T cells, NK cells; recovery of virus-specific cytotoxic T lymphocytes, CTLs) [8]. Incidence of reactivation in patients after HCT is presented in table VII.

The highest risk of CMV recurrence and CMV disease is reported for HCT CMV-seropositive recipients (R), regardless on donor (D) serostatus. The odds ratio for CMV recurrence is higher for R+ vs R- CMV-serostatus transplants (odds ratio: OR=8.0), D-/R+ vs D+/R+ CMV-serostatus transplants (OR=1.2), unrelated/mismatched vs matched-family donor transplants (OR=1.6), and acute graft-versus-host-disease vs others (OR=3.2) [8].

The highest risk for EBV reactivation and development of EBV-PTLD is in the case of donor seropositivity, as in majority of cases EBV-PTLD after HCT is of donor origin [7].

In several studies, the relative frequency of herpes viruses reactivations was analyzed in population of patients after allo-HCT, sometimes also with frequency of other latent viruses. Schmidt-Hieber et al. [17] showed in CNS (patients with encephalitis) incidence of 1.2% (32/2628), including: HHV6, 19%; EBV, 19%; HSV, 13%; JCV, 9%; VZV, 6%; ADV, 3%; more than one virus, 16% (CMV+HHV6+JCV; HHV6+HHV7; CMV+HHV6; HSV+EBV; CMV+VZV+HSV+EBV). The 1-year survival of patients after viral encephalitis was below 40%.

Table VIII. Diagnostics of reactivation and disease after HCT

Diagnostics	CMV	EBV	HHV6	VZV
Material for screening	Blood (p/s)	Blood (p/s)	No screening	No screening
Material for diagnosis disease	Blood (p/s), CNS fluid, Biopsy specimen	Blood (p/s), CNS fluid, Biopsy specimen	Whole blood (p/s); (+hair follicles, nails for CIHHV6); CNS fluid	Blood (p/s), CNS fluid
Diagnosis of reactivation	PCR	PCR	PCR	Clinical + PCR
Most frequent disease manifestations	Pneumonia, GI tract	PTLD	Encephalitis	Varicella/Zoster
Biopsy	Required for proven diagnosis (except retinitis)	Required for proven diagnosis	Not required	Not necessary
Definitive diagnosis	Biopsy (CMV proteins)	Biopsy (EBER, viral proteins)	HHV6-DNA in CSF; exclusion of CIHHV6	Clinical symptoms +DNA-emia
Imaging	Various	PET	Brain MRI often normal	No
Additional methods	DNA-emia (PCR)	DNA-emia (PCR)	DNA-emia (PCR)	Clinical + PCR

p/s (plasma/serum); PET (positron emission tomography); CNS (central nervous system); other abbreviations in text.

Table IX. Possibilities of prophylaxis

Prophylaxis	CMV	EBV	HHV6	VZV
Non-specific prophylaxis	Selecting CMV-matched donor	Selecting EBV-negative donor	Not known	Avoiding contact
Specific prophylaxis	Used as a strategy	Weak recommendation	Not recommended	Mandatory in IgG+ (allo ≥12 months; auto 3-6 months)
Method	Antivirals: GCV (ganciclovir), LMV (letermovir)	Anti-CD20	NO	Acyclovir (valaciclovir)
Possible passive immunization after exposure	CMV-Ig	Not available	Not available	VZ-Ig

Wu et al. [18] also analyzed the incidence of viral CNS reactivation of herpesviruses, with overall incidence of 12.4%. The most frequent were as follows: EBV, 57.1%; HSV1, 19.0%; CMV, 14.3%; VZV, 4.8%, and mixed 4.8% (EBV+CMV).

Polish analyses [19–21] showed the incidence of viral reactivation in children: CMV, 29.2%; EBV, 24.3%; BKV, 22.8%; ADV, 5.2%, and the incidence of HHV6 was 1.5%; however, this virus was not usually being tested in all centers. The respective incidence in adults' patients included the following: CMV, 24.7%; BKV, 5.9%; ADV, 2.9%; EBV, 1.9% [21].

Diagnostics before HCT: serology

Because of incidence and several strategies of prophylaxis and preemptive therapy, it is an universal agreement expressed in a number of guidelines, that in allo-HCT setting, both recipient and donor should be tested serologically (i.e., IgG antibodies) for CMV and EBV, while not for HHV6 and VZV markers. In auto-HCT setting, only CMV serology is usually required, but not EBV, HHV6, or VZV markers. Principles of diagnostics of reactivation and end-organ disease are shown in table VIII. The definitive diagnosis of reactivation is confirmed by the presence of viral DNA detected by PCR. In case of HHV6, one must exclude CIHHV6, while in case of VZV diagnosis is usually clinical.

The proven diagnosis of herpes virus end-organ disease must be done from biopsy in case of CMV and EBV, from the presence of CSF DNA in case of HHV6, and clinical diagnosis with blood DNA for VZV.

Prophylaxis

With the variety of viruses, there is a variety of evidences on viral prophylaxis (Tab. IX). Only in case of CMV, there is a good quality of evidence to use antivirals. Nevertheless, so far it was not a recommended strategy because of its toxicity of antiviral drugs. Introduction of letermovir might possibly change this practice, what is happening already in many centers in other countries [22].

Passive immunization (specific immunoglobulins) is available for CMV (CMV-Ig) and VZV (VZ-Ig), whereas it is not available for EBV and HHV6. VZ-Ig is recommended for prophylaxis after exposure (up to 2 years after HCT) in IgG-negative transplant recipients [5]. CMV-Ig is recommended as an option only for treatment of CMV pneumonia, whereas it is not recommended for prophylaxis or preemptive treatment [22].

Preemptive approach

Preemptive approach is currently recommended as a post-transplant strategy for CMV and EBV reactivation, whereas it is not recommended for HHV6 and not necessary for VZV infection. This approach is a result of frequency of reactivations and therapeutic

Table X. Treatment of end-organ disease

Treatment	CMV	EBV	HHV6	VZV
Treatment (first line)	GCV/FSC	Anti-CD20 +reduction of IST	GCV/FSC	ACV
Treatment (second line)	CDV GCV+FSC		FSC/GCV GCV+FSC	VACV, brivudin, famciclovir
Treatment (resistant cases)	GCV+FSC CDV	+chemotherapy		FSC; CDV (weekly; +probenecid)
Cellular therapy: Cytotoxic T-lymphocytes	CMV-CTL*	EBV-CTL* (Tabelecleucel)	HHV6-CTL*	NO
Off-the-shelf CTLs	Yes*	Yes*	Yes*	
Multi-specific CTLs	Yes (CMV, EBV, HHV6, ADV, BKV)*			

** limited availability; GCV (ganciclovir); FSC (foscarnet); CDV (cidofovir); (V)ACV (val)acyclovir); IST (immunosuppressive therapy); other abbreviations in text.*

Table XI. Impact of herpes virus infections on transplant outcomes

Outcome	CMV [22, 33, 34]	EBV [7, 35, 36]	HHV6 [14–16]	VZV [5, 37]
OS (overall survival)	Decreased OS	No effect	Decreased OS?	Decreased OS
RI (relapse incidence)	No effect	Replication: ↓RI?	No effect	No effect
NRM (non-relapse mortality)	Replication: ↑NRM	Replication: ↑NRM?	Replication: ↑NRM?	
Acute GVHD	No?	No?	YES (↑ in CIHHV6)	No
Chronic GVHD	↑ in repeated CMV infections	Increased (if: donor IgG+)	No?	No

possibilities: antivirals for CMV (ganciclovir GCV and foscarnet FSC in first/second line, and cidofovir CDV in third line of therapy) [22], and anti-CD20 for EBV (rituximab) [23]. Preemptive therapy (also known as preemptive prophylaxis) should be based on a routine screening for blood DNA-emia by qPCR and administration of drugs in case of positive viremia, usually defined locally by specific cutoff value. It is recommended to start preemptive approach within first 4 weeks after HCT and to continue it at least up to day +100 or longer in case of risk factors for reactivation or presence of graft-versus-host disease and immunosuppressive therapy.

Treatment

The first-line treatment of end-organ disease is based on administration of GCV (2 x 5 mg/kg) or FSC (2 x 90 mg/kg) for CMV disease, rituximab 375 mg/m^2 weekly for EBV disease, GCV or FSC for HHV6 disease, and acyclovir (3 x 500 mg/m^2 intravenously or 5 x 800 mg; pediatric dose 4 x 20 mg/kg orally) (Tab. X) [5, 6, 22, 23].

Vaccination

VZV is the only herpes virus for which vaccine is available/approved: live attenuated (LAZV: Zostavax, and LAVV: Varivax), heat-inactivated (V212; Phase III) (auto-HCT) [24], and recombinant (Shingrix; approved 2017; RZV, Phase III, ZOE-HSCT Trial) (presented during EBMT Annual Meeting 2019). So far, live attenuated vaccines are contraindicated both after allo- and auto-HCT at least up to 24 months after HCT. Afterwards, one dose of LAVV can be considered in VZV-seronegative adult patients (two doses in children) with no GvHD, without immunosuppressive treatment, no relapse of underlying disease, and no treatment of immunoglobulins during the previous months; the second dose can be considered in adult seronegative patients or had no history of VZV infection [25–29]. In transplant setting, inactivated vaccines should be preferred to LAVZ. Still, more data are needed on allo-HCT [25–29].

Outcome of infection

Herpes virus infection is always regarded as a serious complications. The most frequent end-organ diseases have relatively poor outcome, with about 50% survival for CMV pneumonia, 70% for EBV-PTLD, and 50% for HHV6 encephalitis [30–32]. Only in case of VZV, the outcome is close to 100%; this is because of effective prophylaxis with acyclovir for at least 12 months after HCT. Positive risk factor for good outcome of infection is reduction of immunosuppressive treatment, if possible. On the other hand, another pitfalls of treatment of herpes virus infection are adverse events of antiviral therapy.
Herpes virus infections might have also an impact on transplant outcomes. The results are ambiguous. The summary, based on large studies, is presented in table XI.

Conclusions

Because of high worldwide seroprevalence and latency, infections with herpesviruses are, and will be, frequent. Current strategies of management of CMV and EBV are based on mandatory monitoring of DNA-emia and administration of preemptive therapy if DNA-emia is positive; however, pharmacological prophylaxis is a renewed possibility in case of CMV (letermovir) and is an option for EBV infection (rituximab). In case of HHV-6, no routine screening is

recommended; however, in case of encephalitis, encephalopathy, myelosuppression, respective diagnostics should be performed, including test for CIHHV6. Finally, with acyclovir prophylaxis, it seems that VZV is under control of transplantologists and hematologists, and there are also possibilities for vaccination against this infection.

Authors' contributions/Wkład autorów

JS – the only author

Conflict of interest/Konflikt interesu

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The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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