Hematopoietic Cell Transplant

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hematopoietic cell transplantation CMV

1. Introduction

Infections are a major threat for morbidity and mortality for patients undergoing hematopoietic stem cell transplantation (HCT). Infections create a main obstacle to the success of HCT, along with relapsed malignancy and graft-versus-host disease (GVHD) and finally might compromise the benefit of transplantation. However, the continuous progress in development of preventive strategies and regimens were introduced and became available [1]. Major etiological cause of infections are bacteria, fungi, viruses, and parasites. Viral infections are most frequently diagnosed in patients after allo-HCT, both in children and adults [2][3][4].

Viruses causing infection after allo-HCT can be divided as typically latent (mainly herpesviruses) or sporadic (mainly respiratory viruses) in nature [5]. The third group include hepatotropic viruses. Following primary infection, herpesviruses establish latency in infected individuals in the host cells and may reactivate upon external stimuli and during periods of immunosuppression. The sporadic or episodic infections are typically acquired after exposure rather than as being a result of a reactivation event [1]. The viral pathogenesis has a significant impact on the type of preventive antiviral strategy.

2. ECIL Guidelines

This review is based on European Conference on Infections in Leukemia (ECIL) recommendations, which were developed between ECIL2 (2007) and ECIL8 (2019) editions. The ECIL is a common initiative of the Infectious Diseases Working Party of the European Society for Blood and Marrow Transplantation (EBMT), the Infectious Diseases Group of the European Organization for Research and Treatment in Cancer (EORTC), the Supportive Care group of the European LeukemiaNet, and the Immunocompromised Host Society (ICHS). Objectives of ECIL are: to elaborate European guidelines on prophylaxis, and treatment of infectious complications in leukemic patients; to obtain information about what are current management strategies in Europe; to favor communication between groups; and to define new areas of clinical research. The first edition of ECIL was held in 2005, and then it became biannual meeting, dedicated to selected topics. ECIL uses CDC-based grading system of

recommendations, slightly modified during subsequent editions. To unify these differences, in this paper the simplified system of recommendations was adopted (Table 1).

Table 1. Grading system of recommendations.

STRENGTH OF A RECOMMENDATION
• Grade A: ECIL strongly supports the recommendation for use • Grade B: ECIL moderately supports the recommendation for use • Grade C: ECIL marginally supports the recommendation for use · Grade D: ECIL is against the use of the recommendation
QUALITY OF EVIDENCE
• Level I: evidence from at least one properly designed randomized, controlled trial • Level II: evidence from at least one well designed clinical trial, without randomization; from cohort or case-controlled analytical studies (preferably from more than one 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

3. Principles of Antiviral Management after HCT

Preventative and therapeutic antiviral strategies for the most threatening viruses in HCT setting are discussed in the following sections of this review. The basic concepts of dealing with viral infections include: pre-transplant risk assessment, universal and specific antiviral prophylaxis, monitoring viral infections after transplant with possibility of pre-emptive treatment, and therapy of established viral infections. Screening for reactivation and its monitoring with option of using preemptive treatment and/or application of specific antiviral prophylaxis in seropositive recipients plays a role in preventing infection and/or disease caused by latent herpesviruses such as cytomegalovirus (CMV), Epstein–Barr Virus (EBV), Human Herpes Virus 6 (HHV-6), and varicella zoster virus (VZV).

Assessment of pre-transplant risk can be considered for many viral infections. The risk can be assessed both in donors and recipients. There is a possible risk of transfer of some viral infections from donor. The risk of viral infections that might be transmitted with the graft from the donor is well-known in case of herpesviruses CMV, EBV, and HHV-6; hepatotropic viruses HBV and HCV; as well as in case of HIV, HTLV-1/2, and West Nile virus. Other viruses that give viremia include influenza, adenovirus, and parvovirus B19. Assessment of pre-transplant risk is an important tool that can be used for management decisions pre-, peri-, and post-transplant. It can either be used for diagnosis of antibodies (e.g., CMV, EBV, VZV), or the virus (e.g., community acquired respiratory viruses; CARV), or both (e.g., HBV).

World-wide using strategies both by donor registries, and transplant centers require pre-transplant risk assessment and screening patient for: HIV, HBV, HCV, CMV, EBV, VZV, HSV (most of them are also legally required); and screening donor for: HIV, HBV, HCV, CMV, EBV, HTLV-1, and HTLV-2. Many centers additionally, just before admitting the patient to the ward screen patients for: respiratory viruses including COVID-19, CMV, adenovirus, and norovirus in stool in children.

Strategies of antiviral management include prophylaxis, pre-emptive treatment, and targeted treatment (Table 2). Empirical therapy is not used in antiviral strategies. Prophylaxis can be done at universal (preventive strategy) and specific level. Universal prophylaxis includes non-pharmacologic methods of prevention of infection or reactivation. Risk-adapted specific prophylaxis includes use of specific antivirals or cellular therapy or other specific methods in order to prevent specific infection, in high-risk groups. Pre-emptive therapy means use of therapeutic approaches in asymptomatic infection, detected by a screening assay. Finally, targeted therapy is used in established specific viral end-organ infections. While universal prophylaxis is designed for all patients, for each subsequent strategy the number of patients needed treatment is lower and lower.

Table 2. Strategies for managing viral infection following hematopoietic cell transplantation.

Strategy	Management
General prophylaxis	To prevent viral infection/reactivation
Risk-adapted prophylaxis	To prevent viral infection/reactivation in high-risk subgroups
Pre-emptive treatment	Treatment of (a)symptomatic viral infection detected by a screening assay in order to prevent viral disease
Targeted treatment	Treatment of end-organ viral disease

4. Cytomegalovirus (CMV)

Cytomegalovirus (CMV), classified as the beta human herpesvirus type 5 (HHV-5), is a major cause of serious complications in recipients of allo-HCT [6]. While primary CMV infection in overall healthy individuals is usually asymptomatic, or it manifests as mononucleosis-like syndrome or a self-limited febrile sickness, its reactivation in allo-HCT recipients might be life-threatening [7].

CMV infection directly or indirectly adversely affect transplant outcomes [8]. Direct end-organ toxicity is the harmful effect of the virus itself; indirect CMV toxicity is caused by development of side effects of antiviral therapy and virus-related suppression of the immune system [9]. CMV replication after allo-HCT has been associated with increased non-relapse mortality [10]. Recipient pre-transplant CMV-seropositivity, recipient and donor status, post-transplant CMV reactivation or infection, and CMV disease lead to decrease survival after HCT [10][11][12].

4.1. Prevention of Cytomegalovirus Reactivation and Disease

Donor and recipient cytomegalovirus serological status. In order to prevent primary CMV infection in CMV-seronegative recipient of allo-HCT, donor CMV-match selection, transfusion policy (i.e., tested safe blood products, including leukodepleted and filtered red cell and platelet concentrates) [7]. In pre-transplant phase it is mandatory that all patients and donors are tested for CMV IgG antibodies (AII) [6]. It is recommended to select CMV-seronegative donor for a CMV-seronegative recipient (AI; except haploidentical-HCT: AIII), and CMV-seropositive donor for CMV-seropositive recipient, if possible (BII) [6]. Any strategies permissive for any CMV reactivation with the aim of reducing leukemic relapse are discouraged, since any CMV replication after HCT increases the risk of overall mortality [10].

Cytomegalovirus monitoring. Patients after allo-HCT should be monitored for CMV DNA-emia in plasma or whole blood (AII) by qPCR assays which are more sensitive than detecting viral antigen pp65 (BII) [13], thus being the primary choice for most of transplant centers for monitoring viral load in everyday clinical practice. On the other hand, in case of suspected tissue involvement, the presence of tissue CMV should be documented by histopathology, immunohistochemistry, rapid culture, virus isolation, or DNA hybridization techniques and supported by the absence of other documented causes of pathology. It should be underlined that for a given patient, CMV monitoring should be done with the same method of DNA extraction, the same specimen type and PCR assay. Monitoring should be done at least once weekly for the first 100 days after HCT (AII). Longer monitoring is usually recommended in patients with chronic GVHD, in case of previous CMV reactivation, in patients after mismatched, cord blood, or haploidentical HCT (without post-transplant cyclophosphamide); also in those being on long-term effective prophylaxis, or displaying persistent immunodeficiency (AIII). In spite of progress in PCT standardization, still the threshold of CMV-DNA to start pre-emptive therapy has not been well enough defined in order to be sure to involve all possible clinical situations. CMV DNA threshold values for pre-emptive therapy should be adapted locally according to the monitoring technique used, PCR standardization, and the transplant method (AIII). Immunological monitoring of allogeneic HCT recipients is recommended, at the

minimal level of lymphocyte subpopulations, and preferentially with sequential monitoring of interferon-γ-producing cytomegalovirus-specific T cells (BII) [6].

Prevention of cytomegalovirus replication by systemic antiviral chemoprophylaxis is aimed to prevent CMV reactivation in CMV-seropositive patients. Current pharmacological management strategies to prevent CMV infection (primary or reactivation) or CMV disease in recipient of allo-HCT include prophylaxis or pre-emptive therapy. Prophylaxis is defined as a strategy that antiviral agents is given to a patient either to prevent a primary, reactivated or recurrent CMV infection. Pre-emptive therapy is a strategy where antiviral agents are given for an asymptomatic CMV infection detected by a specific screening assay [6][14].

4.2. Prophylaxis of CMV Infection

Primary prophylaxis. Prophylaxis of CMV infection was usually not preferred option in allo-HCT recipients, because of toxicity of (val)ganciclovir and foscarnet, or low effectivity of (val)acyclovir (Table 3). The use of letermovir (LMV), a new antiviral drug, has shown improved option of anti-CMV prophylaxis, and probably has changed the landscape of anti-CMV management in HCT setting. LMV is a CMV terminase inhibitor, which was used in a 14-week prophylactic regimen in CMV-seropositive HCT recipients [15]. LMV has reduced clinically significant CMV infection (csCMVi) at 24 weeks without major toxic effects [6]. All-cause mortality has been reduced in patients treated with LMV at 24 and 48 weeks [10][15][16]. The positive effects of antiviral prophylaxis in allo-HCT recipients was confirmed in over 800 patients in real-world analysis [7]. Currently, there might be a rationale for a universal prophylaxis with LMV in all CMV+ recipients (R), since all the categories of patients (low risk, high risk) benefit from the prophylactic effect of LMV including a tendency to lower mortality. Another rationale is that patients might develop severe complications from CMV infections despite not being regarded as high risk.

Table 3. Recommendations for antiviral pre-emptive treatment for cytomegalovirus (CMV) viremia.

Intervention	Prophylaxis	Pre-Emptive Treatment	
		First Line	Second Line
LETERMOVIR	AI		
GANCICLOVIR 10 mg/kg/day divided in two doses; maintenance dose 5 mg/kg/day for 7–14 days, until PCR negativity.	CI	AI	AII (if not used in first line therapy)
FOSCARNET 180 mg/kg/day in 2–3 doses	DII	AI	AII (if not used in first line therapy)
VALGANCICLOVIR	CII	AII	
COMBINATION THERAPY (GANCICLOVIR+ FOSCARNET)		DIII	CII

Intervention	Prophylaxis	Pre-Emptive Treatment	
		First Line	Second Line
CIDOFOVIR 5 mg/kg, administered weekly. Hyperhydration oral probenecid is mandatory due to risk of acute kidney injury.		-	BII
REDUCTION OF IMMUNOSUPPRESSION		-	BIII
ACYCLOVIR	CI		
LEFLUNOMIDE/ARTESUNATE			CIII
Intravenous immunoglobulins (IVIG)	DI		DIII

Secondary CMV prophylaxis. There is also a rationale for secondary prophylaxis, and for delayed targeted strategy. While we are aware of the good effect of pre-emptive therapy in most standard or low risk patients, still half of the patients who develop one CMV episode will have at least one recurrence. While the first episode of a CMV reactivation is frequently easily managed at least in standard risk patients, it becomes more difficult in clinically resistant cases. Thus, the secondary prophylaxis in patients who have experienced one episode can be considered. It has already been shown that secondary anti-CMV prophylaxis with LMV is a safe and effective approach in a large proportion of patients, targeted at high-risk patients for additional CMV recurrence [17]. However, no prospective controlled trial was performed so far. When primary prophylaxis for CMV+ recipients is the standard, a secondary prophylaxis would have restricted indications: the use after treatment of primary infection (including D+/R-); CMV infection/disease occurring after the end of primary prophylaxis; and patient who did not receive primary prophylaxis with LMV upfront.

4.3. Preemptive Therapy Against CMV Disease

In the year 2019, preemptive therapy is regarded to be the standard strategy for CMV prevention after allogeneic HCT [6][14][18][19]. In preemptive strategy, patients are monitored for CMV reactivation usually by PCR. Detection of asymptomatic CMV reactivation above a “viral load threshold” leads to the introduction of preemptive treatment, in order to prevent CMV disease. Current ECIL7 recommendations for first- and second-line preemptive therapy for allo-HCT recipients are shown in Table 3 [6].

The pitfall of preemptive therapy is that the strategy of viremia-guided preemptive therapy still allows for CMV reactivation. Although preemptive treatment of asymptomatic CMV reactivation is efficacious in reducing tissue invasive CMV disease, emerging data suggest a negative long-term effect of CMV replication [10]. The duration of anti-CMV treatment should be at least 2 weeks, aiming for at least one negative test for presence of CMV. Increasing CMV-DNA-emia within the first 2 weeks of antiviral therapy does not indicate a need of changing the therapy. If CMV is still detected after 2 weeks of therapy, additional maintenance therapy with an antiviral compound given once daily can be considered. Repeated courses of additional pre-emptive therapy or a prolonged initial pre-emptive therapy might be necessary in patients showing slow or delayed decrease in viral load [6].

4.4. Treatment of Cytomegalovirus Disease

Antiviral therapy with intravenous ganciclovir is recommended by ECIL-7 for CMV disease as the first-line option (AII) [6]. Addition of G-CSF can be considered in case of neutropenia to allow prolonged ganciclovir therapy. Foscarnet can be used instead of ganciclovir in case of toxic effects or evidence of antiviral resistance (AIII). No positive effect of standard or CMV-specific immunoglobulins on outcome of CMV infection was shown in any studies, thus its use is rather controversial. There are, however, evidences that addition of IVIG or hyperimmunized CMV-Ig to antiviral therapy can be justified for the treatment of CMV pneumonia (CIII). Intravitreal injections of ganciclovir or foscarnet can be recommended for the treatment of CMV retinitis, usually combined with systemic therapy (BII). Oral valganciclovir can be used alternatively in place of intravenous ganciclovir or foscarnet, with exception of patients with severe gastrointestinal GVHD (BIII). Cidofovir (CDV) or the combination of intravenous ganciclovir and foscarnet are other second- or third-line therapies for CMV disease (BII).

CMV pneumonia. The risk for CMV pneumonia increases with increasing CMV-DNA load; however, a definite threshold value for CMV-DNA load for introduction of beginning treatment of any diagnosis of organ involvement cannot be established. Performing bronchoscopy with broncho-alveolar lavage (BAL) is largely desired diagnostic approach in case of suspicion of CMV pneumonia. A negative CMV-DNA test in the BAL fluid has a high negative predictive value close to 100% and practically excludes the possibility of CMV pneumonia. The cut-off value for blood/plasma CMV-DNA-emia might be differentiated between transplant centers, different patients and specificity of performing the BAL procedure and the CMV-DNA quantitation assay used. Severity of CMV pneumonia can obviously influence on CMV-DNA levels, what may impact the clinical decisions. A CMV-DNA viral load >200 IU/mL in BAL fluid has already a good positive predictive value in diagnosing pneumonia in allo-HCT recipients, while lower levels in BAL might indicate pulmonary shedding. Recommendation for antiviral therapy of CMV pneumonia are presented in Table 4. There is no strictly recommended time of therapy of CMV disease. In case of CMV pneumonia, it is usually 21–28 days of induction therapy, followed by at least 7–14 days of maintenance treatment [6].

Table 4. Treatment of CMV pneumonia.

Intervention	Dosage as in Pre-Emptive Treatment
FIRST LINE OF THERAPY	
Ganciclovir iv (AII)	Therapy of choice for at least 21 days. Dosage: 10 mg/kg/day divided in two doses; maintenance dose 5 mg/kg/day for 7–14 days, until PCR negativity.
Foscarnet iv (AIII)	180 mg/kg/day in 2–3 doses.

CMV-IVIG (CIII)	500 mg/kg every 48 h; 7–10 doses, followed by weekly administration for 2–4 weeks
SECOND/THIRD LINE OF THERAPY	
Cidofovir	Typical dose 5 mg/kg, administered weekly. Hyperhydration oral probenecid is mandatory due to risk of acute kidney injury.
Foscarnet + Ganciclovir (BII)	
Adoptive immunotherapy (BII)	Cytotoxic T-lymphocytes CMV-CTL (VST: viral specific T-cells)

Maribavir was shown to be effective for resistant or refractory CMV disease both in a phase 2 [20] and phase 3 study [21]. No data exist so far to support the use of letermovir or brincidofovir as treatments for CMV disease, and thus no recommendations can be given for these drugs.

Management of CMV infection and disease after auto-HCT. The risk of CMV infection in auto-HCT recipients is 30–50% in seropositive individuals, but in comparison to allo-HCT recipients, the risk of CMV disease incidence and frequency is <1%. The risk of CMV reactivation can be increased in case of CD34-selected patients and in patients receiving anti-thymocyte globulin (ATG) for the treatment of autoimmune disease. Nevertheless, for patients undergoing auto-HCT, routine monitoring and pre-emptive anti-CMV therapy is not recommended (DII). Still, high-risk recipients of auto-HCT, such as patients with autoimmune disease with CD34 selection or those receiving ATG, monitoring and the use of pre-emptive therapy might be beneficial (CII) [6].

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