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How to manage cytomegalovirus reactivation/infection after hematopoietic stem cell transplantation: practical tips for clinicians

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Abstract

Cytomegalovirus (CMV) reactivation is one of the most common and life-threatening complications after allogeneic hematopoietic stem cell transplantation (allo-HSCT). It is associated with an increased risk of transplantation failure, non-relapse mortality (NRM), and lower overall survival (OS) than in patients without CMV reactivation, even in the era of pre-emptive antiviral treatment. Numerous risk factors for CMV reactivation in the setting of allo-HSCT have been identified. Donor/recipient CMV serological status remains the main risk factor influencing the incidence and mortality of CMV disease after transplantation. Proper selection of donor and recipient, regular and careful monitoring, an early intervention in CMV reactivation, and rapid and effective treatment when the disease develops, remain crucial to decrease the risk of post-transplantation CMV reactivation/disease. The introduction of letermovir as CMV prophylaxis has reduced NRM and improved OS.

Herein we present practical tips as to how to manage CMV reactivation/disease after allo-HSCT through an illustrative case report, with a focus on the risk factors present before and during the procedure.

Key words: allogeneic hematopoietic stem cell transplantation, cytomegalovirus reactivation, letermovir, overall survival, non-relapse mortality, prophylaxis

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Introduction

Treatment with high-dose chemotherapy supported by allogeneic hematopoietic stem cell transplantation (allo-HSCT) has significantly improved the prognosis of patients with malignant and non-malignant hematological disorders [1].

However, despite its proven efficacy, the procedure still carries a significant risk of post-transplant complications. Among these, infections are frequent and remain the major cause of increased morbidity and mortality. Viral infections, especially opportunistic, are the leading cause of death in the post-transplant period with a ~30% mortality rate [1–3]. Cytomegalovirus (CMV) reactivation after allo-HSCT is associated with an increased risk of graft rejection, non-relapse mortality (NRM), and decreased overall survival (OS) [4–7].

CMV is a DNA beta herpes virus carried by up to 90% of the adult population worldwide [8]. Its seroprevalence increases with age. After primary infection, typically asymptomatic in immunocompetent people, CMV remains latent for years and can reactivate at any time in immunocompromised patients [8, 9]. This can be particularly observed in patients after chemotherapy, solid organ transplantation (SOT), and HSCT [9–11]. According to recent studies, delayed reconstitution of the immune system, especially

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Table I. Definitions of cytomegalovirus infection and disease (based on [17–19])

Term	Definition
CMV infection	Isolation of CMV or detection of viral proteins or nucleic acid in any body fluid or tissue sample
Primary CMV infection	First confirmed CMV infection in an individual showing no evidence of CMV exposure before transplantation
Recurrent CMV infection	CMV infection in patient with known previous evidence of CMV infection when virus had not been detected for at least four weeks of active surveillance. This may result from reactivation of latent virus or reinfection (*see below*)
CMV reinfection	Detection of a CMV strain distinct from strain that caused initial CMV infection
CMV reactivation	Detection of two CMV strains (prior and current strain) that are found to be indistinguishable either by sequencing of specific regions of viral genome or by molecular techniques that examine genetic polymorphism
Symptomatic CMV infection	Both presence of general symptoms and/or signs (e.g. fever, bone marrow suppression) and detection of CMV genetic material obtained using sensitive methods. No signs of CMV end-organ disease
CMV disease	Presence of symptoms and/or signs from affected organ and detection of CMV by appropriately sensitive testing of tissue samples obtained by biopsy or other invasive technique (Exception: CMV retinitis — findings observed in ophthalmological examination are sufficient confirmation)

CMV — cytomegalovirus

functional CMV-specific T-cell immunity, may cause CMV reactivation and contribute to the development of CMV disease [10, 12, 13]. The highest rate of CMV reactivation has been reported in recipients of allo-HSCT, with a median of 37% [10, 14].

The development of modern techniques focusing on more sensitive and rapid diagnostic assays, together with the introduction of highly effective drugs against CMV, has helped to reduce the incidence of CMV disease and its serious effects [15, 16]. Nevertheless, CMV reactivation/disease remains one of the most common and life-threatening complications after allo-HSCT [16].

CMV infection is defined as the isolation of viral antigens, genetic material, or the virus itself, in any tissue or body fluid sample. The term "recurrent infection" stands for a new CMV infection in a patient with a confirmed history of a previous CMV infection when the virus had not been detected for at least four weeks of active surveillance, and that can result from reinfection or reactivation of the latent virus. All other definitions concerning CMV infections, reactivation and disease are set out in Table I [17–19].

Below we present how to manage CMV reactivation/disease after allotransplantation through an illustrative case report.

Illustrative case (I)

A 40-year-old CMV-seropositive male diagnosed with a high-risk acute myeloid leukemia (AML) had completed induction treatment with a DAC (daunorubicin, cytarabine, cladribine) regimen with no response. Second line chemotherapy with CLAG-M [cladribine, cytarabine, mitoxantrone and granulocyte colony-stimulating factor (G-CSF)] resulted in complete remission (CR).

A 36-year-old, partially human leukocyte antigen (HLA)-matched, CMV-seronegative female donor was identified for transplantation. Both donor and recipient reported no concomitant diseases and shared the same blood group (B Rh–). Following myeloablative conditioning (MAC) with TBF (thiotepa, busulfan, fludarabine), the patient was transplanted with 1.85×10^6/kg of body weight of CD34-positive cells.

Risk factors for CMV reactivation

Numerous risk factors for CMV reactivation in the setting of allo-HSCT have been identified. These factors can be 1) patient-related (age, sex, CMV serostatus); 2) donor-related (age, sex, CMV serostatus, donor type and HLA-match status; 3) transplant-related (type and intensity of conditioning, stem cell source, use of T-cell depletion); and 4) related to post-transplant immune reconstitution.

Among all those mentioned, three factors seem to be crucial for post-transplant outcome: 1) donor (D)-negative/recipient (R)-positive CMV serological status; 2) occurrence/severity of acute/chronic graft-versus-host disease (GvHD) and its treatment; and 3) unrelated (UD) or mismatched donor (MMD) transplant (Table II).

Donor/recipient CMV serostatus before transplantation

D/R CMV serological status remains the main risk factor influencing the incidence and mortality of CMV disease after allo-HSCT [10, 14]. A positive CMV IgM result confirms ongoing or very recent infection and is a contraindication for transplantation. The presence of CMV IgG antibodies indicates previous contact with the virus and immune competence against CMV. Seropositive individuals carry the latent CMV, and their blood components are potentially infectious to CMV-naïve recipients, leading to transfusion-transmitted CMV. Several recent studies have shown

Table II. Risk factors for cytomegalovirus reactivation

Category	Risk factor
Recipient-related	Age
	Sex
	CMV serostatus
Donor-related	Age
	Sex
	CMV serostatus
	Donor type (family/unrelated)
	HLA-match status
Transplant-related	Conditioning regimen (type and intensity)
	Stem cells source
	T-cell depletion use
	Acute and/or chronic GvHD (prophylaxis, occurrence and treatment)
Related to immune recovery	Recovery of CCTLs
	Immunosuppressive treatment (type and duration)
	Prolonged exposure to anti-CMV drugs
	Speed of immune cells recovery

CMV — cytomegalovirus; HLA — human leukocyte antigen; GvHD — graft-versus-host disease; CCTLs — CMV-specific cytotoxic T lymphocytes

that CMV reactivation is most common in CMV IgG seropositive recipients regardless of donor status [14, 20]. These patients are also nearly nine times more likely to develop CMV disease than seronegative recipients [14, 17, 21]. Moreover, it has been demonstrated that CMV seropositive recipients receiving a graft from a seronegative donor have more frequently CMV reactivation after allo-HSCT when compared to D+/R+ [20, 22–24]. This phenomenon could be explained by the transfer of antiviral cytokines and CMV-specific cytotoxic T lymphocytes (CCTLs) along with the graft from seropositive donor [14, 22].

To sum up, patients can be categorised into those having a high risk (D–/R+ or D+/R+), an intermediate risk (D+/R–), or a low risk (D–/R–) of CMV reactivation [25].

Occurrence of acute and/or chronic GvHD

GvHD is a reaction of donor immunocompetent cells against host tissues and it occurs after HSCT. Two forms of GvHD can be seen: acute and chronic. The two have different pathophysiologies, but involve similar types of cells. GvHD development, together with immunosuppressive treatment especially with corticosteroids, may prolong T-cell reconstitution after allo-HSCT, increasing the patient's susceptibility to opportunistic infections [9, 26, 27]. CMV is reactivated twice as often in patients with acute GvHD than in those without this complication (60.1% vs. 32.1%) [5, 28, 29]. Moreover, patients who experience severe acute GvHD have been shown to be at a much higher risk of CMV infection compared to those with mild severity (92.3% vs. 51.9%) [10, 30, 31]. On the other hand, it has been demonstrated that CMV reactivation increases the risk of death from GvHD [32, 33].

Unrelated (UD) or mismatched donor (MMD) transplant

CMV reactivation risk is higher in UD and MMD transplants compared to a matched sibling donor (MSD) transplant. The risk of CMV disease is ~3 times greater in UD/MMD grafts than in MSD, especially if the recipient is CMV-seropositive [14, 28, 34–36].

Several scoring systems based on the presence of risk factors have been proposed to date, although none has been validated for use in clinical practice [10, 37].

Case continued (II)

GvHD prophylaxis consisted of tacrolimus (TAC), methotrexate (MTX) and anti-thymocyte globulin (ATG). The patient engrafted neutrophils and platelets on days +13 and +17 post-transplant, respectively. On day +18, the patient developed an erythematous, maculopapular rash on <50% of his body surface (grade II aGvHD). Symptoms resolved rapidly after pulses of intravenous methylprednisolone (MP) at 2 mg/kg of bw and topical corticosteroids. Due to the increased serum creatinine level, TAC was switched to mycophenolate mofetil (MMF). Bone marrow assessment performed on day +28 revealed CR with negative minimal residual disease (MRD) and full donor chimerism. CMV was negative on polymerase chain reaction (PCR). Two days later, the patient was discharged on MMF and routine antiviral/antibacterial prophylaxis.

Post-transplantation work-up and CMV prophylaxis

Post-transplant strategy is based on regular monitoring of CMV viremia in peripheral blood. The following diagnostic techniques are used in clinical practice: CMV pp65 antigenemia assay or, preferably, quantitative polymerase chain reaction (qPCR).

It is vital to use the same monitoring technique, PCR assay and sample type for a given patient [18]. CMV tests/viral load monitoring should be performed regularly, at least once a week during the first 100 days for both pre-emptive therapy and during letermovir (LMV) prophylaxis. Until more data on the issue of delayed CMV reactivation/disease is available, some authors postulate that patients with a high risk of CMV reactivation should be provided with prolonged LMV prophylaxis (after day +100) and CMV monitoring at least monthly over the six months after their HSCT. Longer monitoring is also recommended in patients after mismatched, cord blood or haploidentical transplantation, in

those with acute or chronic GvHD, or after prior CMV reactivation or if suffering from an immunodeficiency disorder [18]. PCR assays should be calibrated according to current standards [38].

A real time PCR test determines the amount of CMV genetic material in one milliliter of plasma or serum, and even though this value should be expressed in international units of the viral genome per milliliter [IU/mL], the use of [copies/mL] is still acceptable [39, 40].

It is worth noting that CMV disease can occur with any level of viremia and it is crucial to minimize the risk of CMV replication by the introduction of appropriate prophylaxis [4, 17, 41]. The preventive measures in stem cell recipients include both prophylactic and pre-emptive treatment (PET). Prophylactic treatment is recommended for high-risk patients before any evidence of CMV infection/reactivation occurs. The mainstay of primary prophylaxis is proper donor selection based on the CMV status of donor and recipient. Namely, for a seronegative recipient, a seronegative donor must be sought as the first-line option. For a seropositive recipient, a seropositive donor remains the choice [18]. Matching negative donors to positive recipients should be avoided. Other preventive strategies include a proper transfusion policy of CMV-negative, leukodepleted blood products [11, 42, 43].

The search for the safest and most effective prophylactic agent has been going on for years. Prior therapies have demonstrated numerous adverse effects when used prophylactically [42, 44]. LMV was approved in 2017 by the US Food and Drug Administration (FDA) for the prevention of CMV infection/disease in adult CMV-seropositive allo-HSCT recipients [42, 45]. LMV belongs to a new group of compounds that inhibit the CMV DNA terminase complex disrupting viral genome formation and the maturation of virions. It has been demonstrated in a phase III study that LMV compared to a placebo improved post-transplant survival and decreased CMV-related mortality, and without myelosuppression as a side effect [42].

The positive results from this phase III study have been also confirmed in a real-world setting. Real-world data shows significant improvements in reducing the risk of any CMV viremia and clinically significant CMV infection in studies. CMV primary prophylaxis with LMV has been shown to be effective in reducing the risk of all-cause and non-relapse mortality 200 days after allo-HSCT, and in improving OS during the first 24 and 48 weeks after HSCT [17, 42, 46–48].

LMV not only presents high efficacy and safety in preventing CMV reactivation in seropositive patients, but it also delays the onset of clinically significant CMV infection and at the same time does not delay granulocyte reconstitution. The clearest effect has been seen in high-risk patients.

LMV is a drug that changes the paradigm of PET use in favor of prophylaxis as first-line management strategy against CMV [7, 47, 49]. A Polish experience with LMV prophylaxis, published recently, confirms its low toxicity with no myelosuppressive (or any other) adverse effect and good tolerability [50]. Our own experience with more than 30 patients treated with LMV seems to confirm its efficacy and safety (data not published).

Primary prophylaxis with LMV should be started before day 28 after transplantation and continued for the first 100 days at a single dose of 480 mg per day (or 240 mg during concomitant use of cyclosporine) in the case of seropositive patients. In those with multiple risk factors of CMV reactivation/infection (e.g. seropositive and treated with escalated immunosuppression due to aGvHD), prolonged LMV prophylaxis after day +100 should be considered. Since LMV is active solely against CMV, acyclovir/valacyclovir prophylaxis against other common viruses (herpes simplex and varicella zoster) is required [18]. One should be aware of CMV DNAemia 'blips' that occur frequently after allo-HSCT (with ~32% prevalence), particularly in patients receiving a graft from CMV-seropositive donors and LMV prophylaxis. They are associated with a lower incidence of CMV end-organ disease [51]. A viral 'blip' is defined as an episode of isolated positive PCR test result where both the previous and the subsequent test, performed with seven days, remain negative. Blips could be either an artefact, or a reflection, of transient low-level CMV replication [51, 52]. In the case of first CMV PCR positive samples, blips should always be considered, and ongoing replication must be confirmed before starting anti-CMV treatment.

Case continued (III)

After discharge from hospital, our patient continued immunosuppressive therapy with oral MMF. During check-ups, weekly monitoring of CMV viral load level was continued, and virus remained negative. The symptoms of GvHD were absent and immunosuppressive treatment was gradually reduced. LMV was not reimbursed for Polish patients at that time, and so this medicine was not given despite the presence of unfavorable prognostic factors. On day +64, the patient was urgently readmitted with symptoms of intestinal acute GvHD accompanied by pulmonary infection. Prior CMV assessment had been done a week before and remained negative, making the primary diagnosis of GvHD more likely. On admission, the patient was in a poor condition overall: he presented with nausea, appetite loss, general weakness, and persistent cough. Physical examination was unremarkable except for cachexia. Peripheral blood picture showed pancytopenia. Recurrence of leukemia was ruled out. Laboratory tests revealed hyperbilirubinemia of 31 µmol/L, elevated liver and pancreatic enzymes [alanine aminotransferase (AlAT) = 388 units/L, glutamyl transpeptidase (GGTP) = 179 IU/L, amylase = 83 units/L, alkaline phosphatase = 96 units/L) as well as elevated C-reactive protein (CRP) (115 mg/L). *Clostridioides difficile* infection

was excluded. Blood culture was negative for any bacterial or fungal pathogens. *Mycoplasma pneumoniae* and *Pneumocystis jirovecii* assays were also negative. CMV by qPCR was as high as 14,386 copies/μL in the serum sample and CMV reactivation was confirmed. After CMV confirmation, immunosuppressive treatment was de-escalated. Colon biopsy was not performed due to the patient's worsening overall condition and the high risk of complications.

Clinical manifestations

CMV reactivation is typically reported within the first 100 days after allo-HSCT and is seen mostly in patients not receiving CMV prophylaxis. Late CMV reactivation (up to two years after HSCT) occurs mainly in patients with profound immune suppression, especially after prolonged exposure to anti-CMV drugs, after prophylaxis/PET discontinuation, or during chronic GvHD [11, 18, 23].

In the general population, apart from non-specific fever or mononucleosis-like syndrome, no clinical signs of CMV infection occur [14, 18, 19]. In immunosuppressed patients, a latent infection can reactivate and CMV replication may lead to life-threatening end-organ disease. The incidence of CMV disease in the early post-HSCT period is estimated to be 5–7% in high-risk transplant recipients. Early CMV disease most commonly presents with gastrointestinal (GI) involvement and CMV gastroenteritis/colitis accounts for more than 90% of clinical manifestations [18, 42, 52].

Interestingly, CMV gastroenteritis often develops without detectable CMV DNAemia, making a diagnosis challenging, especially in terms of differentiating from intestinal GvHD. Sometimes these two manifestations will overlap, and a tissue biopsy is necessary [53–56]. Another frequent CMV disease manifestation is CMV pneumonia, defined as the detection of CMV in bronchoalveolar lavage fluid (BAL) or a lung biopsy together with clinical signs/symptoms of pneumonia. Bronchoscopy with BAL is the recommended diagnostic procedure in suspected CMV pneumonia. There is no definitive cut-off value for CMV DNA load in BAL, but quantitative PCR can be used to distinguish CMV-induced pneumonia (viral load of >200–500 IU/mL) from asymptomatic pulmonary shedding (viral load lower than 200 IU/mL) [18]. BAL fluid negative for CMV DNA has a negative predictive value of nearly 100%, and practically rules out CMV pneumonia.

Late CMV disease occurs in up to 15% of high-risk patients, mostly in the form of interstitial pneumonitis [18, 57]. Other frequent CMV disease manifestations are hepatitis, retinitis, encephalitis, and bone marrow suppression [18]. Prophylactic strategies used in the early post-transplant period increase the risk of late CMV disease in up to 25% of patients by delaying the recovery of CMV-specific T-cells [10, 56, 58]. It is well-documented that the greater the viremia the worse the prognosis, but even a relatively low viral load affects the outcome negatively [4].

Case continued (IV)

Starting from day +65, treatment with intravenous ganciclovir (GCV) at 5 mg/kg of bw was implemented, and immunosuppressive treatment and low doses of methylprednisolone and MMF were continued. One week later, the patient presented with a 38°C fever with chills, persistent, non-productive cough, and malaise. Chest X-ray depicted massive pneumonia; high-resolution computed tomography (HRCT) showed bilateral diffuse ground glass infiltrates with interlobular septal thickening. Bronchoscopy with bronchoalveolar lavage was performed and CMV DNA of 502 copies/mL was detected in the BAL, and GCV treatment was continued.

Six days after readmission, the patient's condition rapidly deteriorated with dyspnea and oxygen saturation of 85% despite maintained antiviral treatment. Increasing inflammatory parameters, deepening pancytopenia, and progressive respiratory insufficiency were observed. The patient died on day +72 after transplantation amid symptoms of cardiopulmonary and multiorgan failure.

Treatment and management

Pre-emptive treatment

Despite an attempt to harmonize and standardize CMV-DNA measurements made in 2010 by the World Health Organization (WHO), there is still no universal CMV-DNAemia threshold at which PET should be initiated [19, 40].

The obtained results vary and depend not only on the test sample (plasma or whole blood) but also on the experience of the transplant center. Monitoring of plasma CMV DNA load kinetics with evaluation of viral load doubling time may offer a clue as to when to start therapy. It has been suggested that in those with a doubling time <2 days, therapy should be started [18, 59, 60]. In high-risk patients, it is recommended to start PET at a lower viral load, i.e. >150 IU/mL, and in low-risk patients at >500 IU/mL [58].

According to the 2017 European Conference on Infections in Leukemia (ECIL-7) recommendations, intravenous GCV at 5 mg/kg of bw twice daily or foscarnet at 60 mg/kg of bw twice daily show comparable efficacy and should be offered as first-line PET [18, 61]. The oral form of GCV — valgancyclovir (VGCV) 900 mg twice a day — is also acceptable except for patients with severe intestinal GvHD. Treatment should last for a minimum of two weeks and be continued until CMV PCR negativity. GCV or foscarnet are also recommended for maintenance treatment. In second-line PET, an alternative drug to that used in the first line should be given. Cidofovir at 3–5 mg/kg of bw weekly can also be recommended, with special caution regarding renal function. Administration of intravenous immunoglobulins (IVIg) is not recommended [18].

For the treatment of symptomatic CMV disease, the therapeutic armamentarium is similar to that available for PET [62]. Therapeutic doses of anti-viral agents should be continued until CMV PCR negativity, but then a 4-week maintenance should be considered. Of note, an increase in viral load observed during the first seven days after treatment initiation does not prove its ineffectiveness or drug resistance [18]. Therefore, discontinuation of therapy in such a situation is not justified. It is also worth noting that starting treatment at a lower CMV viral load results in faster elimination of the virus, which reflects the treatment efficacy and prevents the induction of drug resistance [17, 18, 58].

CMV resistance to antivirals should be considered if therapy has failed after more than three weeks of treatment. A persistent or increasing CMV antigenemia/DNA load or escalating organ manifestations of CMV disease may indicate the development of either clinical or viral resistance. Clinical refractoriness is observed when CMV DNA levels in blood or plasma increase by >1 log10 after at least two weeks of appropriately selected and properly administered antiviral drugs, and clinical resistance occurs when CMV disease symptoms worsen after two weeks of suitable antiviral therapy. Viral resistance is defined by the presence of known mutations that reduce the virus's sensitivity to one or more antivirals. Genetic testing is recommended when the CMV viral load does not decrease by >1 log10 after more than two weeks of properly applied therapy. It is also advised when the plasma viral load exceeds 1,000 IU/mL. It has been demonstrated that mutations in UL97 are mainly responsible for GCV resistance. When resistance is clinically suspected, its type needs to be confirmed, the drug class should be switched, and immunosuppression should be reduced if possible. The choice of drug for a confirmed mutation should be based on the type of mutation, previous exposure to drugs, and acceptable toxicity profile. If high doses of GCV are required, pre-emptive administration of filgrastim (G-CSF) should be considered. Combination therapy is not recommended due to the lack of data confirming its efficacy, with the risk of cumulative nephrotoxicity and myelotoxicity of these drugs [55, 56].

Regarding the issue of managing drug-induced toxicity, experts do not recommend monitoring (V)GCV levels, as peak plasma levels do not correlate with either clinical efficacy or myelotoxicity. In cases of acute kidney failure, the drug dosage should be adjusted, and other potentially nephrotoxic medications should be reduced. In cases of neutropenia, reducing the drug dose when treating active CMV infection is not recommended considering the risk of drug resistance developing. Instead, G-CSF should be used, (V)GCV should be replaced with foscarnet, and myelotoxic drugs such as MMF should be temporarily reduced, replaced, or withdrawn [53].

Conclusions and future directions

The following steps would decrease the risk of post-transplantation CMV reactivation/disease: proper selection of donor and recipient; regular and careful monitoring; an early intervention in CMV reactivation; and rapid and effective treatment when disease develops [1, 58].

The use of PET has resulted in a decline in the incidence of CMV-related end-organ disease and this has translated into better post-transplantation outcomes [18, 61]. To date, LMV prophylaxis (provided at least to day +100) changes the well-established pattern of CMV management policy in seropositive patients from monitoring and pre-emptive therapy to a preventive approach [17, 46].

Although the available anti-CMV drugs have demonstrated efficacy in preventing and managing post-transplant CMV infection, the risk of toxicity and resistance limits their long-term use [63]. Hence, there is a constant need for newer, safer therapies to be developed. Adoptive cell therapy (ACT), by transferring virus-specific donor T-cells to an immunocompetent recipient, has come into use as a rational approach to induce rapid and sufficient viral immunity in patients until they achieve optimal immune reconstitution. However, obstacles such as regulations, logistics and time-consuming virus-specific T-cell selection techniques, limit the widespread implementation of this therapy. CMV vaccines remain under development [18, 53, 64].

Several novel drugs are currently in development. Maribavir is one of them, and is active against CMV including strains resistant to GCV or foscarnet. It was approved by the FDA in 2021 and in November 2022 by the European Medicines Agency (EMA) for the treatment of recurrent CMV infection and/or disease after the failure of at least one prior therapy in adult transplant patients. In a randomized phase III study (NCT02931539), oral maribavir at a dose of 400 mg twice daily showed high efficacy with significantly lower renal toxicity and neutropenia rates. A phase III randomized trial determining the utility of extended (i.e. beyond day 100 from transplant) LMV prophylaxis (#NCT03930615) and a single-center phase II study of LMV use in relapsed/refractory CMV infections (#NCT03728426) are underway. Promising results from a phase II study of posoleucel (#NCT04693637) were unveiled at the 64th American Society of Hematology (ASH) Annual Meeting in 2022. This study evaluated the efficacy and safety of posoleucel in preventing clinically significant viral infections caused by six target viruses, including CMV. It investigated both prophylaxis in patients at high risk of viral reactivation, and PET in those experiencing viral reactivation. As a result, a significant reduction in clinically significant viral infections and also a long-term effect of the drug on the expansion of functional CMV-specific T-cells accompanied by a decrease in viral load were observed. This study has progressed to phase III (#NCT05305040) for further evaluation [65].

Authors' contributions

MW — collected data and wrote manuscript. GH — co-wrote manuscript, critical revision.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

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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