

Review

Management of cytomegalovirus infection in allogeneic hematopoietic stem cell transplants



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ABSTRACT

Cytomegalovirus (CMV) is a common infection encountered in immunocompromised patients. It is associated with high morbidity and mortality, particularly in patients undergoing allogeneic (allo-) haematopoietic stem cell transplantation (HSCT). This review presents the most recent management strategies for CMV infection in allo-HSCT recipients. Pre-emptive treatment (PET) consists of frequent monitoring of CMV polymerase chain reaction (PCR) after HSCT; this has been the standard of care for prevention of CMV for many years, given the potential drug toxicity associated with the traditional drugs used as prophylaxis. However, letermovir, recently approved as a chemoprophylactic agent for prevention of CMV, has shown great efficacy in randomized clinical trials and real-world data. Treatment of CMV disease is becoming increasingly difficult, and must take into account the patient's risk profile and the potential for CMV drug resistance. Different treatment strategies exist for refractory and resistant CMV disease. Maribavir is a new drug that showed promising results in the treatment of refractory and resistant CMV disease. Other alternative treatments, such as cellular adoptive immunotherapy, artesunate and leflunomide, may play an adjunctive role in the treatment of challenging cases; however, further investigation is warranted.

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Introduction

Cytomegalovirus (CMV) is notorious for causing severe infections and complications in immunocompromised patients, particularly those undergoing allogeneic (allo-) or autologous (auto-) haematopoietic stem cell transplantation (HSCT). Active CMV infection, defined as the presence of CMV DNA in plasma or whole blood, may develop in up to two-thirds of allo-HSCT recipients in the first 100 days following transplant. If left untreated, it may progress to end-organ disease in 25–30% of cases, such as pneumonia, colitis and retinitis [1,2]. CMV infection has also been associated with increased risk of superimposed bacterial and fungal infections [3,4]. There are many risk factors that contribute

to CMV reactivation. Seropositive recipients receiving grafts from seronegative donors are at the highest risk [5–9], probably due to delayed reconstitution of functional CMV-specific T-cell responses following ablation [10,11]. In addition, myeloablative regimens containing T-cell-depleting agents, such as alemtuzumab and antithymocyte globulin, increase the risk of CMV reactivation and end-organ disease [12–14]. Finally, the association between CMV and graft-versus-host disease (GvHD) is thought to be bidirectional. Immune reconstitution delay secondary to GvHD, and CMV's encoded proteins with immunosuppressive and pro-inflammatory properties may trigger GvHD [15,16]. Interestingly, recent observations showed that patients with HLA B*07:02 and those with a higher count of invariant natural killer T-cells had a significantly lower cumulative incidence of CMV reactivation [17,18]. This review will discuss new developments in management strategies of CMV infection in allo-HSCT recipients.

2. Pre-emptive CMV treatment

Pre-emptive treatment (PET) consists of monitoring CMV viral load by polymerase chain reaction (PCR) once weekly until day +100 after transplantation, and initiating antiviral treatment once viraemia is detected at a certain pre-specified threshold. PET may also be guided by checking pp65 antigenaemia assay, which

Abbreviations: AIDS, Acquired immunodeficiency syndrome; Allo-, Allogeneic; Auto-, Autologous; CMV, Cytomegalovirus; CMVIG, CMV hyperimmunoglobulin; CNS, Central nervous system; CSCM, Clinically significant CMV infection; GvHD, Graft-versus-host disease; Haplo-, Haploidentical; HSCT, Haematopoietic stem cell transplantation; IFN- γ , Interferon-gamma; PCR, Polymerase chain reaction; PET, Pre-emptive treatment.

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may require a shorter duration of therapy as antigen clearance is quicker than DNA clearance [2]. The aim of this strategy is to prevent progression to CMV end-organ disease while sparing the adverse effects and cost of chemoprophylaxis. In certain high-risk patients – including those with pretransplant CMV disease; those receiving a T-cell-depleted graft, an umbilical cord graft or HLA-mismatched grafts; or patients taking alemtuzumab – experts recommend twice-weekly monitoring [19]. Monitoring is usually required until day +100 after transplant; however, it may be extended beyond day +100 in patients with a history of CMV infection during the first 100 days, those with mismatched-HLA or unrelated donors, those receiving glucocorticoids for GvHD, and those with low CD4 counts or low CMV-specific T cells if checked. However, there is no consensus about the PCR threshold that should be used as the basis to initiate anti-CMV drugs in the PET approach. In high-risk patients, it is usually recommended to initiate treatment for a CMV DNA level ≥ 1500 IU/mL in the first 100 days post-HSCT. However, in one study, initiating treatment at lower thresholds (< 350 IU/mL) in allo-HSCT recipients was shown to reduce the median peak viraemia compared with higher thresholds (≥ 350 IU/mL) [821 IU/mL (interquartile range 302–1633 IU/mL) vs 2930 IU/mL (interquartile range 1200–11,314 IU/mL); $P < 0.0001$] [20].

In the absence of a consensus regarding a specific threshold of CMV viraemia that would indicate the initiation of PET, the risk of progression to clinically significant CMV disease should be considered to guide the management. Determining CMV-specific T-cell immunity may help guide the decision to initiate PET as low immunity has been associated with increased risk of CMV disease. Several assays can assess CMV-specific T-cell immunity, such as enzyme-linked immunosorbent spot assay (ELISpot), flow cytometry with intracellular cytokine staining and tetramer staining [21]. The use of ELISpot has been shown to help determine the risk of progression to CMV disease [22]. However, these assays are not widely available for clinical use, require trained personnel and have high costs. An interferon-gamma (IFN- γ) release assay for CMV, the QuantiFERON-CMV, has been developed with the goal of assessing the host's CMV-specific T-cell immunity. It has shown high rates of agreement with ELISpot and may be of valuable clinical use [23].

A study including patients undergoing allogeneic HSCT with high risk of CMV disease (R+ and/or D+) assessed use of the QuantiFERON-CMV assay to predict the risk of progression to CMV disease. The magnitude of IFN- γ production before HSCT and CMV reactivation, disease and spontaneous viral control after HSCT were not correlated. However, there was a significant association between CMV disease at 3 months after HSCT and a lower magnitude of IFN- γ production in the QuantiFERON-CMV assay after HSCT. This association remained significant after excluding D+/R-recipients who are at a lower risk of CMV reactivation and disease. Both the quantitative QuantiFERON-CMV assay results and the qualitative results (reactive, non-reactive, indeterminate) were associated with CMV clinical outcomes. Spontaneous viral control was observed in 49%, 0% and 10% of participants with reactive, non-reactive and indeterminate results, respectively ($P < 0.001$). A reactive QuantiFERON-CMV result was also associated with a lower peak CMV PCR and spontaneous viral control [23]. Another study monitoring the evolution of CMV-specific T-cell response using the QuantiFERON-CMV assay also showed that patients who did not achieve CMV-specific immune reconstitution were found to have a higher incidence of CMV reactivation [24]. Although not approved by the US Food and Drug Administration for clinical use to date, the QuantiFERON-CMV assay shows promising potential as an adjunct tool for assessing the risk of progression to CMV disease, and determining the indication for initiation of PET in the absence of clear thresholds for the CMV PCR test.

In view of the adverse effects reported for traditional drugs used for CMV prophylaxis, PET has been the recommended strategy for prevention of CMV disease in HSCT recipients for years [25]. Moreover, outcomes were reported to be similar with PET when compared with primary prophylaxis. For instance, a double-blind, randomized, multi-centre clinical trial found that valganciclovir prophylaxis (900 mg orally once daily) was not superior to PCR-guided PET in allo-HSCT recipients at reducing late CMV disease invasive infection-free survival after HSCT, fungal infections or death. In addition, more subjects received haematopoietic growth factors in the valganciclovir group (25% vs 12%; $P = 0.026$) [26]. PET was also shown to decrease the incidence of CMV end-organ disease by 10% in allo-HSCT recipients [27,28].

Once PET is initiated, the duration of therapy is usually 2 weeks until a negative CMV PCR is achieved. The duration of treatment may be extended in patients who do not clear the viraemia after 2 weeks of treatment [29]. It should be noted that, during monitoring with weekly PCR testing, some patients may experience transient 'blips' of CMV DNAemia defined as an isolated positive low titre on CMV PCR testing that is preceded and followed by a negative PCR result [30]. It is unclear whether these transient episodes of DNAemia are associated with worse outcomes, and if they should prompt the initiation of treatment [31]. A recently published retrospective study investigating the effect of blips on the outcomes of allo-HSCT recipients found that blips may occur in up to 25% of patients, mostly when the donor is seropositive. The median CMV DNA load in patients with blips was found to be substantially lower than the DNA load detected on the first positive PCR sample of patients with prolonged viraemia. In addition, a threshold of 48 IU/mL predicted progression to prolonged viraemia, with sensitivity of 66% and specificity of 70.2% [32]. Thus, it is prudent to monitor CMV replication if blips are suspected before rushing to start antiviral therapy.

Many antiviral agents are available for use as PET; their mechanism of action is illustrated in Fig. 1. Ganciclovir is the most commonly used drug [29]. It is a synthetic nucleoside analogue that inhibits DNA viral polymerase and thus inhibits viral replication [33]. Ganciclovir is given at a dose of 5 mg/kg intravenously (IV) every 12h. Valganciclovir is the prodrug of ganciclovir, and can achieve the same therapeutic drug levels when given at a dose of 900 mg orally twice daily [34]. In fact, many studies have shown that valganciclovir is as effective as ganciclovir as PET in allo-HSCT recipients, and may even decrease the length of hospitalization due to its oral availability [35–37]. However, myelosuppression is frequently associated with (val)ganciclovir use [38,39]. A study showed that low marrow cellularity, hyperbilirubinaemia, and elevated creatinine > 1.2 mg/dL were risk factors associated with (val)ganciclovir-related neutropenia in allo-HSCT recipients. In that same study, neutropenia was demonstrated to be an independent negative factor for overall survival and event-free survival, and a risk factor for treatment-related mortality [39]. In order to mitigate the adverse effects without compromising efficacy, the dose of (val)ganciclovir can be reduced and the treatment course can be shortened [40–42]. Foscarnet 60 mg/kg IV every 12h and cidofovir 5 mg/kg per week, both viral DNA polymerase inhibitors, can be used as second- and third-line agents for PET, particularly when myelotoxicity is an issue. However, nephrotoxicity, electrolyte abnormalities and infusion-related nausea are major reported side effects. In a study on solid organ transplant (SOT) and HSCT recipients, nephrotoxicity was reported to vary between 24% and 71% at the end of foscarnet therapy, and long-term toxicity reached 41% [43]. To avoid nephrotoxicity, the dose of foscarnet should be adjusted to the estimated creatinine clearance, alongside adequate IV hydration and avoidance of concomitant nephrotoxic drugs. Treatment interruption may be considered in the event of evidence of nephrotoxicity.

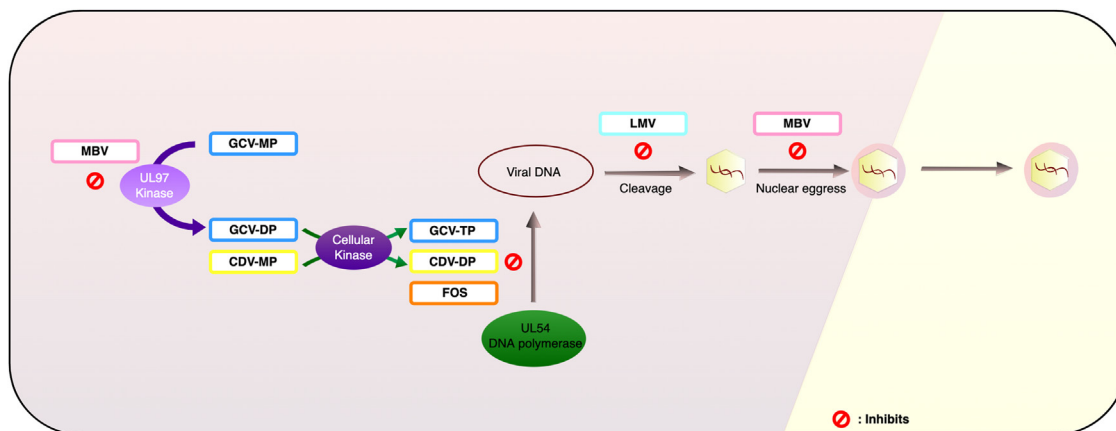


Fig. 1. Mechanism of action of anti-cytomegalovirus antivirals. GCV-MP, ganciclovir monophosphate; GCV-DP, ganciclovir diphosphate; CDV-MP, cidofovir monophosphate; CDV-DP, cidofovir diphosphate; FOS, foscarnet; LMV, letermovir; MBV, maribavir.

Maribavir is a benzimidazole riboside that inhibits CMV UL97, and halts viral maturation and egress [44]. It has shown a good safety profile in terms of myelosuppression and nephrotoxicity in phase 1 trials and does not require dose adjustment. Reported side effects include nausea, vomiting and diarrhoea [45]. Subsequently, in a phase 2 trial comparing maribavir with valganciclovir as PET following HSCT or SOT, given for a median of 45 days, 62% and 79% of patients in the maribavir group had an undetectable viral load at 3 and 6 weeks, respectively, compared with 56% and 67% for the valganciclovir group. The rate of recurrence of CMV viraemia at any time during the trial was similar in both groups [46]. However, after successful phase 1 and 2 trials, maribavir failed to show efficacy in the initial phase 3 trial at reducing CMV infection compared with placebo at either day 100 or 6 months after allo-HSCT [47]. Thus, maribavir is still not recommended as PET for CMV reactivation.

PET certainly offers advantages as it lowers drug costs and toxicity while allowing for regulated CMV replication, which may result in early immune reconstitution. However, it requires compliance and cooperation from patients for routine laboratory visits. It is unclear if PET will continue to be used in centres where novel effective drugs are available for prophylaxis.

3. CMV prophylaxis

Primary chemoprophylaxis is desirable to prevent CMV reactivation in high-risk patients, including CMV-seropositive recipients, seronegative recipients who receive T-cell-depleted graft from a seropositive donor, recipients of an HLA-mismatched donor, and patients who receive alemtuzumab or post-transplant cyclophosphamide [48–50]. Ganciclovir was the traditional drug given for prophylaxis, at a dose of 5 mg/kg IV twice daily for the first week followed by 5 mg/kg IV once daily [51]. However, its use did not reduce mortality, and was associated with high incidence of neutropenia and high rates of secondary bacterial and fungal infections [52,53]. Valganciclovir can also be used for CMV prophylaxis at a dose of 900 mg daily [26]. Thus, new drugs were sought for CMV prophylaxis.

Letermovir is an antiviral agent that inhibits CMV replication by binding to components of the terminase complex (UL51, UL56 or both), but it has no activity against other herpes viruses. It should be administered with other antivirals such as valacyclovir when used for primary prophylaxis for various herpes viruses. It was approved in November 2017 by the US Food and Drug Administration for primary CMV prophylaxis in CMV-seropositive recipients after allo-HSCT at a dose of 480 mg/day (or 240 mg/day

in patients taking cyclosporine) [54]. It is offered as oral and IV formulations, enabling treatment during periods when patients are critically unwell and unable to tolerate oral intake. The approval of letermovir represents a significant advancement because it does not cause myelotoxicity or nephrotoxicity, and it does not require dose modification for mild-to-moderate hepatic and renal impairments. In the phase 3 trial, the incidence of clinically significant CMV infection at week 24 after transplantation was significantly lower among letermovir recipients [122/325 (37.5%)] compared with placebo [103/170 (60.6%)], with no reported increased risk of myelotoxicity [55]. In addition, the largest real-world data study published to date, including 204 patients from 17 centres in Italy, found a cumulative incidence of clinically significant CMV infection (CSCI) in allo-HSCT recipients of 5.4% at +100 days and 18.1% at +168 days, which is comparable to the registration trial (7.7% and 17.5%, respectively) [56]. Furthermore, other real-world experiences with smaller cohorts reported markedly reduced incidence of CSCI in allo-HSCT recipients who received letermovir as primary prophylaxis compared with patients who did not receive prophylaxis [57,58]. Despite these positive outcomes, breakthrough CMV infection may occur while patients are on letermovir prophylaxis. Hence, DNAemia surveillance with PCR should be continued for at least 6 months after HSCT, even if letermovir prophylaxis is being used [59]. To date, only one small retrospective cohort study of 26 patients identified gastrointestinal GvHD and low-grade CMV replication (21–149 IU/mL) as risk factors for breakthrough infection [60]. Nevertheless, it should be noted that patients on letermovir prophylaxis seem to have a non-negligible risk of late CMV reactivation, reaching up to 13% [56]. A recent retrospective study including 333 allo-HSCT recipients found improved overall survival and non-relapse mortality during the first 100 days, but increased late reactivation and worse CMV-related mortality between day 180 and day 364, especially in patients with CMV IgG serum levels <400 mg/dL (hazard ratio 3.19, 95% confidence interval 1.29–7.92) [61]. In fact, this risk may be increased after discontinuation of letermovir due to delayed CMV-specific cellular immune reconstitution in patients taking prophylaxis [62]. Such reports have raised the possibility of extending letermovir prophylaxis beyond 100 days after transplant. Currently, a phase 3 clinical trial is investigating the efficacy and safety of letermovir prophylaxis for 200 days after transplant instead of the conventional 100 days [63]. Overall, with its efficacy at preventing CSCI, good safety profile and cost-effectiveness [64,65], letermovir is commonly a preferred agent for CMV prophylaxis.

Moreover, letermovir prophylaxis was shown in many instances to reduce the incidence of resistant or refractory CMV disease

[29,66]. A retrospective single-centre study reported that patients who received letermovir as primary prophylaxis after HSCT had a significantly lower incidence of resistant/refractory CMV disease (2% vs 11%; $P=0.001$) and a much lower incidence of CSCI (17% vs 53%; $P<0.0001$). Additionally, multivariate analysis showed that letermovir primary prophylaxis was an independent protective factor against the development of resistant/refractory CMV disease. Also, CMV end-organ disease, CMV peak viraemia, and use of foscarnet and its resulting nephrotoxicity and non-relapse mortality were all reduced [67].

Therapeutic drug monitoring is a valuable tool in the assessment of response to various antimicrobial agents, particularly in immunocompromised patients, those on other medications and those with comorbidities. In a prospective study by Royston et al., therapeutic drug monitoring was performed 3 and 7 days after initiating letermovir and weekly thereafter. The study found no association between trough serum concentrations (C_{trough}) of letermovir and the presence of any gastrointestinal symptoms, including nausea, vomiting and severe diarrhoea. On the other hand, C_{trough} was significantly higher in patients with acute GvHD of grade 2 or higher (median C_{trough} 499 vs 293 $\mu\text{g/L}$; $P=0.004$). The authors also found significantly higher letermovir C_{trough} in patients taking posaconazole (707 vs 259 $\mu\text{g/L}$; $P<0.001$); systemic corticosteroids, especially prednisone (median C_{trough} 555 vs 215 $\mu\text{g/L}$; $P<0.001$); and cyclosporine (437 vs 248 $\mu\text{g/L}$; $P=0.01$). The association remained significant on multivariate analysis for posaconazole and cyclosporin, indicating that they may be independent risk factors for higher letermovir C_{trough} . Conversely, the use of multiple antibacterial drugs and antiemetics did not alter serum concentrations significantly. These findings indicate that oral letermovir may achieve effective serum concentrations even in patients with gastrointestinal GvHD. The high concentrations seen in patients with GvHD was irrespective of gastrointestinal or non-gastrointestinal GvHD; hence, given the findings, is possibly due to concomitant treatments for GvHD (antifungals and immunosuppressant agents). In fact, both posaconazole and letermovir use the P-glycoprotein metabolism pathway, which may explain the higher levels of letermovir that are observed with concomitant use of posaconazole. In view of the high likelihood of co-administration of these two agents in high-risk HSCT recipients, the implications of these differences in serum concentrations should be considered. However, variations of letermovir serum concentrations were not associated with breakthrough clinically significant CMV infection or new onset of CMV DNAemia. The latter finding should be interpreted with caution in view of the small sample size of this study [68].

Maribavir was evaluated as a potential drug for CMV prophylaxis. A phase 2 multi-centre randomized controlled trial was conducted to evaluate its safety, tolerability and anti-CMV activity when given as primary prophylaxis for CMV-seropositive allo-HSCT recipients. Patients were randomized to three dosing regimens (100 mg twice daily, 400 mg once daily and 400 mg twice daily) and plasma concentration was measured. Results showed that maribavir prophylaxis was safe and effective at reducing CMV antigenaemia and plasma DNAemia by 70%. Interestingly, the need for PET with ganciclovir was reduced significantly, thus sparing adverse effects such as neutropenia. The adequate dose was determined to be 100 mg twice daily as it achieved similar anti-CMV activity compared with higher doses [47]. However, in the phase 3 trial, maribavir failed to show any superiority to placebo in preventing CMV disease when started after engraftment. Although maribavir showed a significant reduction in CMV antigenaemia, there was no significant reduction of CMV PCR [47]. Despite its very safe profile with very few serious side effects, there are insufficient data at present to support the use of maribavir as prophylaxis in HSCT recipients.

4. Treatment of CMV disease

CMV end-organ disease in HSCT recipients mainly affects the lungs, gastrointestinal tract and retina, but cases of central nervous system (CNS) infection and even appendicitis have been described [69]. Historically, ganciclovir has been considered the first-line therapy for CMV end-organ disease, whether it is CMV pneumonitis, colitis or retinitis, despite the lack of controlled trials [29]. In fact, there is no consensus on the modality of treatment of CMV end-organ disease in HSCT recipients, and data are limited to case reports and case series. The low incidence of CMV end-organ disease in HSCT recipients in the era of prophylaxis and PET may have contributed to the lack of rigorous evidence. The lack of population-specific studies has prompted clinicians to extrapolate the data from other immunocompromised patients, notably patients with acquired immunodeficiency syndrome (AIDS) [29]. Stepdown therapy to oral valganciclovir can be done once the patient is stable with no major gastrointestinal problems interfering with its absorption [34]. Foscarnet is used in patients with severe myelosuppression or those who develop neutropenia on ganciclovir therapy. Close monitoring of kidney function is recommended. As for the newer antivirals, there is currently no evidence to recommend the use of letermovir or brincidofovir (novel oral lipid conjugated nucleotide analogue, prodrug of cidofovir [70]) for the treatment of CMV end-organ disease. Recently, a phase 3 trial was completed comparing maribavir 400 mg twice daily with valganciclovir for the treatment of first episode of asymptomatic CMV infection in HSCT recipients, with the primary outcome measure being clearance of viraemia by 8 weeks of treatment [71]. Finally, it is worth mentioning that CMV hyperimmunoglobulin (CMVIG) has been shown, in older studies, to play an adjunctive role in the treatment of CMV disease. Combination therapy of CMVIG and ganciclovir has been shown to improve survival after CMV pneumonitis and enteritis in allo-HSCT, when given adjunctively two to three times per week compared with treatment with anti-CMV drugs alone [72]. In fact, this combination has been also shown to be safe and effective for the treatment of CMV viraemia post allo-HSCT, particularly in patients receiving high-dose antithymocyte globulin [73]. The proposed mechanism of efficacy includes the ability of antibodies to neutralize CMV and block specific cytotoxic T-lymphocyte effector cells, thereby modifying the immunologic response and resultant tissue damage [74,75]. CMVIG is not widely available in many countries at present, therefore limiting its use in clinical practice. Important issues related to management of CMV disease in particular locations are discussed below.

4.1. CNS infections

The majority of the available data on management of CMV CNS infections are derived from patients with AIDS. For instance, a literature review on CMV encephalitis demonstrated that most reported cases occurred in patients with AIDS, and dual antiviral therapy with ganciclovir and foscarnet was the most widely used treatment regimen [76]. It is postulated that this approach may optimize treatment by achieving higher levels in the cerebrospinal fluid, and targeting unidentified CMV mutations in the case of viral compartmentalization [77–79]. Given the absence of guidelines, it is recommended that CMV CNS infections should be treated with a combination of ganciclovir (5 mg/kg every 12 h) and foscarnet (90 mg/kg every 12 h) as induction therapy until clinical improvement and viral suppression are reached. Although limited data exist on cidofovir, combination treatment with cidofovir and foscarnet successfully treated a case of encephalitis with retinitis caused by ganciclovir-resistant CMV with limited nephrotoxicity [80]. In the event of adverse events or treatment intolerance, either dose reduction or monotherapy with either agent may be

considered. Induction therapy should be followed by maintenance therapy with ganciclovir 5 mg/kg every 24 h or transitioned to oral valganciclovir at 900 mg/day. Unlike CMV treatment in patients with AIDS, no guidelines exist on the duration of either induction or maintenance therapy, and management should be tailored to each patient. Adoptive cellular therapy has also been reported and shows promising results in the case of resistant CMV encephalitis [81]. Secondary prophylaxis may also be used after suppression of CMV viral load to prevent recurrence of CMV end-organ disease, which has been described in up to 50% of cases [82]. Secondary prophylaxis has been recommended for patients with a history of CMV disease 6 months prior to HSCT and a history of recurrent CMV infection. In those patients, letermovir may be the safest option given its favourable safety profile [83]. One study from the French Compassionate Programme including 80 CMV-seropositive HSCT recipients with at least one prior episode of CMV infection or disease since HSCT reported that only four patients (5%) had breakthrough infection, of which three were found to have resistant CMV [66]. In patients with AIDS, secondary prophylaxis can be discontinued safely once immune reconstitution is achieved, but in HSCT recipients, there remains little to no evidence as to when to discontinue secondary prophylaxis [84]. The French Compassionate Programme reported that letermovir secondary prophylaxis was used for a median of 118 days (range 26–396 days), while an interim analysis of a single-centre, open-label study including 20 patients taking letermovir for secondary prophylaxis showed a 20% rate of CMV reactivation after 14 weeks of treatment [85].

4.2. Pneumonia

Most studies on the management of CMV pneumonia have been conducted on SOT recipients. The diagnosis of CMV pneumonia may be clinically challenging as the gold standard for diagnosis relies on histopathological evidence of CMV infection on lung biopsy, which may not always be feasible, especially in severely ill patients [86]. Although CMV viral culture or PCR performed on respiratory samples may yield positive results, they may commonly represent viral shedding rather than infection. There are no cut-offs for CMV PCR on respiratory samples [87]. Although one study reported that a cut-off of 4545 IU/mL had sensitivity of 91% and specificity of 77%, only lung transplant patients were included and the findings might not be generalizable to HSCT recipients [88]. In patients with HIV, for example, CMV PCR on bronchoalveolar lavage was found to have much lower sensitivity, barely surpassing 60% [89]. The diagnosis of CMV pneumonia relies on a holistic consideration of clinical, biological, microbiological and radiographic findings.

Once the diagnosis of CMV pneumonia is decided, the mainstay of treatment, also based on non-randomized trials, consists of IV ganciclovir (5–10 mg/kg per day) [74,90–92]. Given the high mortality of CMV pneumonia, studies have investigated the addition of IV immunoglobulins IVIG or CMVIG to the standard ganciclovir. It should be noted that immunoglobulins are recommended as an adjunct to antivirals for CMV pneumonia alone [29], despite some successful attempts in other CMV diseases [93].

4.3. Gastrointestinal tract infections

CMV gastrointestinal disease is the most common manifestation of CMV end-organ disease in HSCT recipients [55,55,94]. It most often manifests as colitis, although reports of oesophagitis, enteritis and even appendicitis have been published [95]. Treatment starts with an induction period with IV ganciclovir, followed by maintenance therapy where patients may be transitioned to oral valganciclovir. It should be noted that transition to oral valganciclovir may

be hindered by reduced absorption. This is commonly observed in cases of severe disease or concomitant gastrointestinal GvHD. The treatment duration is usually no less than 2–4 weeks of induction IV therapy at a dose of 5 mg/kg every 12 h, followed by several weeks of maintenance therapy [65]. The duration of treatment should be individualized, guided by resolution of clinical symptoms and viral eradication on PCR testing when the initial test was positive [96].

4.4. Retinitis

Although less common than gastrointestinal disease in allo-HSCT recipients, CMV retinitis is associated with high morbidity and mortality [97–99]. Treatment of CMV retinitis consists of systemic antivirals, but may also be combined with intravitreal antivirals [100]. The addition of intravitreal ganciclovir at a dose of 1 mg weekly has been associated with improved aqueous opacity, diminished area of the lesion under fundoscopy, and significantly decreased viral load in the anterior aqueous humor until 1 month after the initiation of treatment [101]. The duration of therapy is usually guided by clinical response.

5. Refractory and resistant CMV

Refractory and resistant CMV infection are associated with worse outcomes in HSCT recipients. Compared with non-refractory infection, refractory and resistant CMV infection is more likely to progress to end-organ disease and cause higher mortality [102]. Resistant CMV infection is defined by the presence of a viral genetic mutation that confers resistance to one or more antiviral agents that are known to be active against CMV. On the other hand, refractory CMV is defined by an increase in CMV viral load despite appropriate antiviral therapy, or by progression of clinical signs and symptoms of end-organ disease (gastrointestinal tract, lungs, retina, CNS). Clinical resistance is mainly secondary to host factors rather than genotypic mutations. Thus, altering antiviral therapy without addressing the host factors could be detrimental to the patient [59]. Refractory CMV disease is more common than resistant CMV disease and can occur any time following HSCT, as opposed to resistant CMV which is uncommon during the first 6 weeks post-transplant [67,103]. Specific definitions for resistant and refractory CMV have been proposed, mainly for use in clinical trials [104].

5.1. Risk factors

Recognizing the risk factors for development of resistant or refractory CMV disease would prompt early diagnosis and management and minimize mortality [105]. Previous exposure to anti-CMV therapy, prolonged exposure to anti-CMV medication in the presence of a replicating virus, haploidentical (haplo)-HSCT and T-cell-depleted HSCT increase the risk of developing resistant CMV [59]. This does not usually occur during the first 6 weeks of HSCT in patients who have not been exposed to CMV treatment previously, and typically happens within 2–4 months of the onset of CMV infection [103]. Testing for resistance is undertaken with genotypic assays that detect resistance mutations. Testing for resistance is recommended when the CMV viral load fails to decline by more than 1 log₁₀ after more than 2 weeks of appropriate antiviral therapy [106]. Given that the viral susceptibility profile may differ according to tissue site, samples should be taken from a site of end-organ disease if applicable [107]. Additionally, genotypic assays may not detect resistance accurately if CMV viral loads are inferior to 2000 copies/mL [108]. The clinically relevant mutations in CMV genes and its associated drug resistance are presented in Table 1 [104].

Table 1

Cytomegalovirus (CMV) genes associated with resistance to the available anti-CMV viral agents

CMV gene	Associated drug resistance
UL97 kinase	Ganciclovir, valganciclovir, maribavir
UL54 polymerase	Ganciclovir, valganciclovir, cidofovir, foscarnet
UL27	Maribavir (low level)
UL51/UL56/UL89	Letermovir

5.2. Treatment strategies

No controlled trials to define the best practice in treating resistant or refractory CMV disease have been undertaken to date; consensus is based on expert opinion, and management should preferably be guided by an infectious diseases specialist. When resistant or refractory CMV disease is suspected, immunosuppressive agents should be minimized, and antiviral drugs should be switched to a different class awaiting genotypic testing. Fig. 2 summarizes the recommended strategies for treatment of resistant/refractory CMV disease by the American Society for Transplantation and Cellular Therapy [59]. High-dose ganciclovir, foscarnet and cidofovir are the recommended alternative treatments. As mentioned in Fig. 2, mutations in UL97 gene are usually associated with ganciclovir resistance. Switching from ganciclovir to foscarnet is recommended if high-level UL97 resistance mutations are detected (>5-fold increase in ganciclovir IC50). If certain low-level UL97 resistance mutations are found (M460I, C592G, L595W), ganciclovir can be given at a higher dose of 7.5–10 mg/kg IV every 12 h with pre-emptive granulocyte colony-stimulating factors to mitigate bone marrow suppression [96,109,110]. Mutations in UL54 genes usually indicate foscarnet resistance or cross-resistance to foscarnet and ganciclovir, ganciclovir and cidofovir, or to all three drugs. According to the type of resistance, switching to ganciclovir or cidofovir is warranted. When cross-resistance to all three classes of drugs is identified, a combination of foscarnet and high-dose ganciclovir (7.5–10 mg/kg every 12 h) is usually given.

Nevertheless, real-world examples of these strategies have shown inconsistent results. In a study on patients with ganciclovir-resistant or refractory CMV, 66% of patients who received foscarnet had virological clearance and 31% of patients had CMV relapse. Renal dysfunction occurred in 51% of patients and 1-year mortality was seen in 31% of patients [43]. In another study, 66.7% of patients treated with cidofovir failed to clear CMV viraemia and 66.7% died [111]. Therefore, new alternative medications that are more efficacious and less toxic are needed for the treatment of resistant and refractory CMV infection.

5.3. New alternative therapies for resistant or refractory CMV

Maribavir has been tested previously in a phase 2 trial for refractory or resistant CMV infection, as it acts on the UL97 gene. Two-thirds of the patients in this trial achieved an undetectable viral load within 6 weeks with no difference in CMV clearance and no concern about dose-related myelosuppression (dose 400–1200 mg twice daily). However, the probability of recurrence of CMV viraemia at 6 and 12 weeks after becoming undetectable was 23% and 30%, respectively [112]. Subsequently, a phase 3 trial, the SOLSTICE trial, was undertaken to assess the efficacy of maribavir in treating refractory CMV infection (with or without resistance) in SOT and HSCT recipients. Patients were randomized to receive maribavir 400 mg twice daily for 8 weeks or investigator-assigned therapy (IAT), which consisted of mono- or combination therapy with IV ganciclovir, oral valganciclovir, IV foscarnet or IV cidofovir. Overall, 55.7% of the patients in the maribavir group achieved CMV viraemia clearance at week 8, compared with 23.9%

in the IAT group. Better outcomes were found in the maribavir group across pre-specified groups, including HSCT recipients, patients with baseline genotypic resistance to IAT, and patients with refractory (non-resistant) CMV. Also, patients receiving maribavir had lower incidence of neutropenia and acute kidney injury compared with patients in the IAT group [113]. Thus, maribavir was shown to be superior to conventional therapy, and represents a promising treatment for resistant and refractory CMV infection. It is worth mentioning that the UL97 mutations responsible for maribavir resistance do not affect ganciclovir susceptibilities and vice versa. However, one should keep in mind that by inhibiting UL97, maribavir impairs phosphorylation of ganciclovir; as such, these two drug groups should not be administered together as their actions might be antagonized [114]. In addition, studies have suggested that maribavir has limited penetration into the blood–brain barrier, and its use should be avoided in patients with CMV meningo-encephalitis [44].

Currently, there are insufficient data to support the use of letermovir as treatment for CMV disease [29]. Due to concerns about low thresholds for emergence of resistance, it may not be suitable as monotherapy for refractory or resistant disease [115]. One study reported that mono- or combination therapy may be useful in the treatment of resistant and refractory disease for viral loads <1000 IU/mL, but not when the CMV viral load is higher [116].

5.4. Cellular adoptive immunotherapies

Delayed or impaired CMV-specific cellular immune response has been associated with increased risk of CMV infection [117]. Hence, while donor cells engraft to provide long-term immunity, peripheral blood lymphocytes containing CMV-specific T cells or cytotoxic T cells may be infused to manage CMV infection in HSCT recipients [118]. Initially, this strategy was applied as prophylaxis for CMV to protect patients from CMV complications during the first 8 weeks post-transplant [119]. More recently, studies have suggested that adoptive cell therapy may accelerate immune reconstitution, implying a beneficial role in the management of refractory or resistant CMV infection [120].

CMV-specific T cells are usually harvested from the donor if seropositive, or from a minimally or fully matched seropositive donor. Collection is done through leukapheresis, whole blood donation or even cord blood [121,122]. Ultimately, high numbers of CMV-specific T cells are obtained via ex-vivo expansion, but this method is limited by long (10–60 days) and complicated processes. More timely methods (<24 h) exist but produce lower amounts of T cells [123].

Initial data regarding use of CMV-specific T-cell infusion therapy for resistant or refractory CMV disease in patients who lacked CMV-specific CD4 T helper response showed that five of seven patients achieved a non-transient drop in CMV viral load [124]. A newly published retrospective study investigating the efficacy and safety of CMV-specific T-cell infusion for CMV infection following haplo-HSCT showed promising results. Among 190 allo-HSCT recipients, 137 were receiving CMV-specific cytotoxic T-cell infusion for refractory disease while they were treated pre-emptively. Complete response, defined as achievement of an undetectable CMV viral load, occurred cumulatively in 76.8% and 89.5% at 4 and 6 weeks, respectively, and 62.7% of patients who achieved complete response at 4 weeks had no CMV reactivation in the follow-up period [125]. However, cellular adoptive immunotherapies have been limited essentially by the duration of immunity, cost and limited availability [121]. In addition, graft rejection and transplantation-associated microangiopathies have been reported in some cases [126]. In view of the limited randomized clinical trials, this strategy is recommended to be used only as an adjunct therapy, particularly when multi-drug resistance is identified [59].

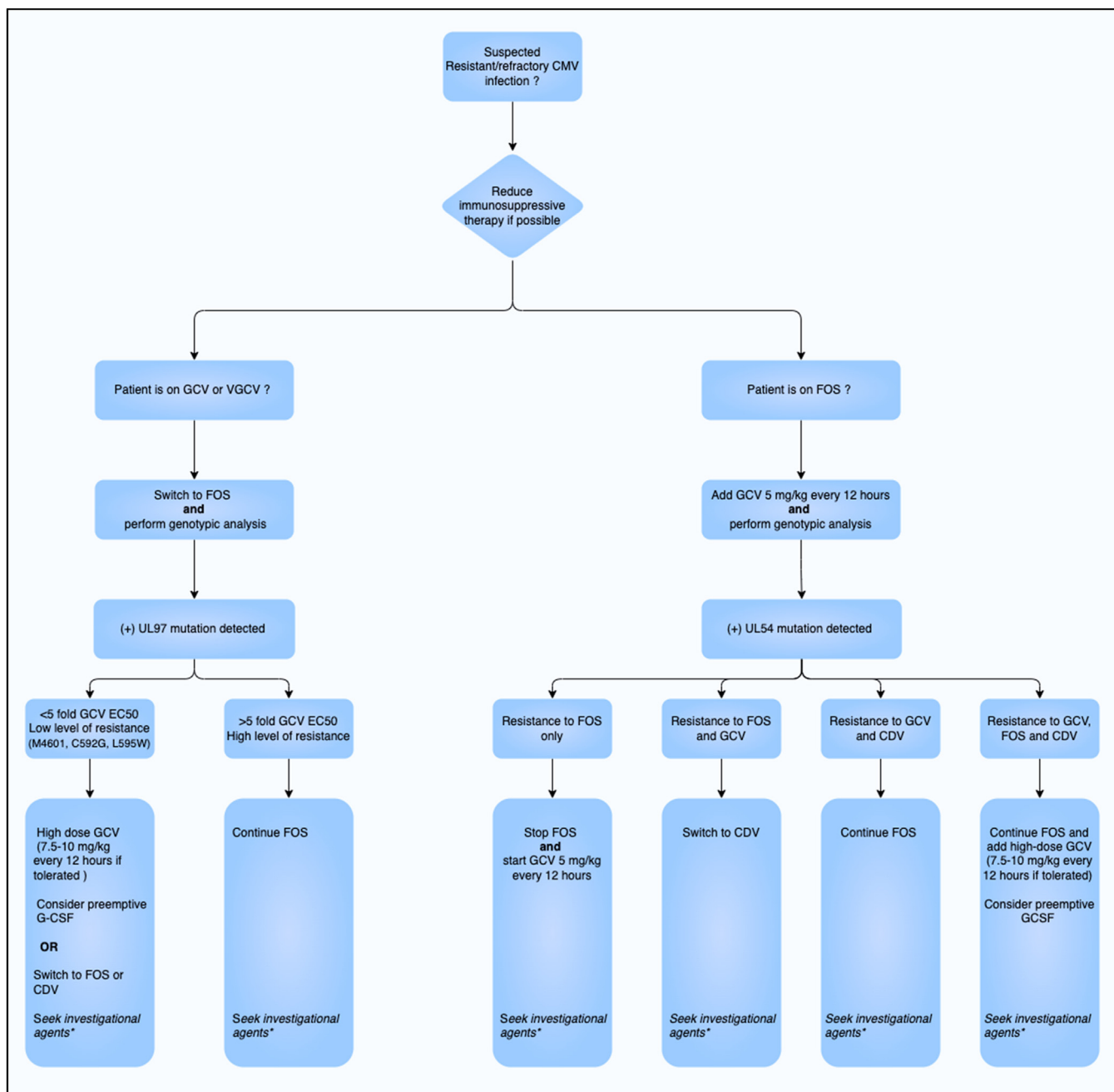


Fig. 2. Recommended strategies for treatment of resistant/refractory cytomegalovirus (CMV) disease by the American Society for Transplantation and Cellular Therapy. FOS, foscarnet; CDV, cidofovir; G-CSF, granulocyte colony-stimulating factor; GCV, ganciclovir; VGCV, valganciclovir. *Maribavir through early access or trial participation for investigational agents, cellular adoptive immunotherapy, leflunomide or artesunate.

5.5. Artesunate and leflunomide

Artesunate and leflunomide interfere with the host cell kinase signalling system required for CMV replication, and both drugs have shown in-vitro activity against ganciclovir-resistant CMV [127,128]. A few reports from the literature showed variable success with leflunomide and artesunate in multi-drug-resistant CMV; however, no controlled clinical trials are available to draw conclusions about their use [129–133]. As such, their use should be limited to optional adjunctive therapy, and drug-related toxicities should be monitored closely.

6. Conclusion

Clinicians dealing with HSCT recipients should apply evidence-based strategies when managing CMV infection. A variety of approaches are currently available for prevention and treatment, including for refractory and resistant disease. Treatment strategies should be personalized and tailored according to patients' risk factors, conditioning regimens received during transplant, and potential CMV drug resistance. The advent of newer agents with favourable safety profiles may render chemoprophylaxis the new standard of care. More real-world data are needed to determine

whether the newly approved drugs will significantly change the traditional treatment strategies for challenging cases of CMV disease.

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