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Transplant/Immunocompromised Hosts (M Morales, Section Editor)

CMV Infection in Hematopoietic Stem Cell Transplantation: Prevention and Treatment Strategies

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Abstract

Purpose of Review Cytomegalovirus (CMV) remains a major cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (Allo-HSCT). New strategies and methods for prevention and management of CMV infection are urgently needed. We aim to review the new developments in diagnostics, prevention, and management strategies of CMV infection in Allo-HSCT recipients.

Recent Findings The approval of the novel anti-CMV drug letermovir in 2017 has led to an increase in the use of antiviral prophylaxis as a preferred approach for prevention in many centers. Real-world studies have shown efficacy similar to the clinical trial. CMV-specific T cell-mediated immunity assays identify patients with immune reconstitution and predict disease progression. Phase 2 trials of maribavir have shown its efficacy as preemptive therapy and treatment of resistant and refractory CMV infections. Adoptive T cell therapy is an emerging option for treatment of refractory and resistant CMV. Of the different CMV vaccine trials, PepVax has shown promising results in a phase 1 trial.

Summary CMV cell-mediated immunity assays have potential to be used as an adjunctive test to develop individualized management plan by identifying the patients who develop immune reconstitution; however, further prospective interventional studies are needed. Maribavir and adoptive T cell therapy are promising new therapies for treatment of CMV infections. CMV vaccine trials for prevention are also under way.

Introduction

Human cytomegalovirus (CMV) is a double-stranded DNA virus that belongs to the beta herpesvirus family. After causing primary infection, the virus establishes latency in various leukocytes including monocytes, lymphocytes, and dendritic and CD34+ cells [1]. CMV reactivation can occur after Allo-HSCT during the time of immunosuppression. CMV positive serology has been associated with decreased overall survival and increased non-relapse mortality, and reactivation can cause severe end-organ disease such as pneumonia, colitis, and retinitis [2]. CMV infection has also been associated with increased risk of bacterial and fungal infections and graft versus host disease (GVHD). The increased risk for GVHD may be related to CMV-related immunomodulatory effects [3, 4].

Risk Factors for CMV Disease After Allo-HSCT

CMV serostatus is an important factor that determines outcomes after Allo-HSCT. CMV positive serology has been associated with increased transplant-related morbidity and mortality; recipient positivity having the greatest impact [5]. The survival and non-relapse mortality is worst for CMV seronegative donor/seropositive recipient (D−/R+), followed by CMV seropositive donor/seropositive recipient (D+/R+) [6]. The other risk factors that increase the risk of CMV infection after HSCT include in vivo or ex vivo T cell depletion, high dose steroids, HLA mismatched or unrelated donors, and GVHD [7–11]. The use of high doses of anti-thymocyte globulin (ATG) for in vivo T cell depletion may be associated with lower survival [12]. Myeloablative conditioning regimens are more cytotoxic than reduced intensity or non-myeloablative regimens, but both cause T cell dysfunction. In a study that compared myeloablative vs non-ablative conditioning regimens, the CMV infections were delayed in the non-myeloablative group, but the 1-year incidence was similar in both groups [13, 14]. GVHD also increases the risk of CMV reactivation, especially with the use of systemic steroids [4, 15, 16]. Steroids can impair the immune system by inhibiting T cell activation. The various sources of stem cell grafts include peripheral blood, bone marrow and umbilical cord blood. In an umbilical cord blood transplant, the T cells that are transferred are naïve, and immune reconstitution is delayed. This delay increases the risk of bacterial and CMV infections early after cord blood transplantation [15, 17–19]. A study by Walker et al in patients receiving antiviral prophylaxis did not find any significant

differences in incidence and outcomes of CMV infections between the 3 different sources of stem cells [20].

Bidirectional Relationship Between CMV and GVHD

It is well established that GVHD and immunosuppressive drugs used for its treatment increase the risk of CMV reactivation. CMV may also play a role in increasing the risk for GVHD. CMV infected cells induce the production of IL-6 which induces inflammation and can lead to GVHD. Studies have shown that CMV replication increases the risk of GVHD [4]. Studies have also shown a significant association between CMV positive serology and development of GVHD, with increased transplant-related mortality and decreased overall survival [2, 10].

CMV Diagnostics

CMV Quantitative Nucleic Acid Test (QNAT)

CMV viral load with QNAT (quantitative nucleic acid test) is used commonly to assess for CMV viremia and disease. CMV viral load and its kinetics are good predictors of disease progression and correlate well with symptom resolution and treatment [21]. One of the major limitations of these tests is the lack of standardization among various commercial and laboratory-developed assays. A multi-center study involving 33 centers showed significant variability among various CMV assays [22]. Thus, it is difficult to establish a universal standard viral threshold that would help predict disease progression. Hence, WHO expert committee established an International Standard (IS) for CMV QNAT in October 2010 [23]. Despite implementation of the WHO IS standard, some variability in the test results still remains. This variability could be due to other factors involved in performing the test [24, 25]. Hence, each individual center has to establish their own threshold for preemptive therapy. The utility of CMV viral load in diagnosis of end-organ diseases like pulmonary and gastrointestinal (GI) disease is still being explored. Establishing appropriate thresholds to differentiate between CMV pneumonia and pulmonary shedding in HSCT remains a challenge [26–28]. CMV GI disease may not cause significant viremia in plasma or whole blood. The gold standard for diagnosis of CMV GI disease is the use of histopathology on GI biopsy samples [29]*. A small retrospective analysis showed promising results of performance of quantitative CMV PCR from GI tissue when compared to immunohistochemistry; however, further larger scale studies are needed to establish appropriate thresholds and validate these findings [30].

CMV Antigen

CMV pp65 antigen is a viral structural protein that is detected in peripheral blood leucocytes during an active CMV infection [31]. The CMV antigen assay uses a monoclonal antibody to detect the pp65 antigen. However, this test is laborious, requires immediate processing, and lacks standardization. Since it detects the viral protein in the leukocytes, it is not useful in neutropenic patients [32]. CMV QNAT is preferred over the antigen test for leukopenic patients.

Culture and Histopathology

Viral culture methods include conventional and shell vial assays. Conventional assays assess cytopathic changes in human fibroblasts. Shell vial assays detect antibody to viral antigen. Both these tests are less sensitive and take longer processing times. Histopathology and immunohistochemistry are performed directly on tissue samples, are very specific, and are the gold standard for diagnosis of invasive CMV disease [33, 34].

CMV Prevention

As mentioned previously, CMV serostatus is an important determinant in predicting the risk of post-transplant CMV reactivation and transplant-related morbidity and mortality due to its immunomodulatory effects. CMV-specific IgM and IgG antibodies are used for determination of serostatus. The 2 major approaches to prevention of CMV infection are antiviral prophylaxis and preemptive therapy. Traditionally, a preemptive treatment approach has been preferred over antiviral prophylaxis in the HSCT population in order to avoid drug-induced toxicity including the potential for bone marrow suppression by antivirals.

A preemptive treatment approach involves screening for CMV viral load by PCR weekly, and initiating antivirals upon detection of viremia at a pre-determined threshold, thus preventing progression to end-organ disease. The threshold varies in different centers based on the type of CMV assay and patient risk factors. Preemptive therapy has benefits by limiting drug toxicity and costs and possibly early immune reconstitution by allowing controlled CMV replication. However, it does require intensive CMV PCR monitoring and patient compliance to keep up with laboratory visits. Multiple trials comparing antiviral prophylaxis including acyclovir, valacyclovir, valganciclovir, brincidofovir, and maribavir showed significant decrease in CMV disease but no significant difference in mortality [35–38]. Prophylaxis with antivirals, especially valganciclovir and acyclovir, can cause side effects like cytopenias which can further increase the risk of bacterial and fungal infections [39]. Hence, most centers practiced preemptive therapy until letermovir was approved in 2017.

Letermovir

Letermovir acts by inhibition of the CMV viral terminase complex, thereby inhibiting viral replication. A randomized controlled trial compared letermovir to standard of care preemptive therapy for 14 weeks and showed significantly fewer CMV infections in the prophylaxis group at 24 weeks (37.5 % vs 60%, $p<0.001$), even in the high-risk subgroup [40•]. There was no significant difference in side effects at 48 weeks. There was a trend towards lower all-cause mortality at 24 weeks (10.2% vs 15.9%, $p=0.03$) and 48 weeks (20.9% vs 25.5%, $p=0.12$) in the letermovir group. The incidence of all-cause mortality in patients who received placebo was higher in patients with clinically significant CMV events compared to those without the events (31% vs 18%, $p=0.02$). In the letermovir group, there was no significant difference in all-cause mortality in patients with or without clinically significant CMV events [41]. After the results from this trial, many centers have adopted the use of letermovir prophylaxis to prevent CMV disease after transplantation. The results of this trial have

been replicated in the real world too. A retrospective study of 53 allogenic transplant recipients receiving letermovir prophylaxis for 14 weeks showed efficacy in preventing CMV infection. Seventy percent of the study population was high risk for CMV reactivation due to receipt of T cell-depleted graft or haploidentical donor. The reactivation rate of CMV infection in CMV R+ patients was 5%. In 29 patients for whom the prophylaxis was extended beyond 14 weeks, reactivation rate was 3.4% [42]. Another study of 29 CMV R+ Allo-HSCT patients compared historical controls who did not receive prophylaxis and found the cumulative incidence of clinically significant CMV infection was lower in the letermovir group, 4% vs 59% at 100 days [43]. Many centers have adopted letermovir prophylaxis in high-risk patients. However, its use in the treatment of CMV infection has not been approved and is not currently recommended due to the risk of failure due to its low barrier to resistance.

Letermovir may also have a role as secondary prophylaxis in prevention of delayed CMV reactivation, especially in high-risk population. In the study by Lin et al., there was no CMV reactivation in 14 patients who received secondary prophylaxis with letermovir [43]. In a French compassionate study program, letermovir was used as secondary prophylaxis in 80 Allo-HSCT CMV R+ patients with high risk of CMV reactivation. High-risk criteria were having unrelated or haploidentical donor, use of T cell depleting agents, presence of acute or chronic GVHD, and cord blood transplant. In this study, 60% of patients used T cell depleting agents like alemtuzumab or anti-thymocyte globulin, and 67% had GVHD (all stages). Twenty-two percent of those patients had grade 3–4 GVHD. Four of 80 (5.5%) developed breakthrough CMV infections, one developed letermovir resistance, and 6 deaths were reported [44]. Further prospective studies are needed. A phase 3 randomized clinical trial assessing the extension of letermovir prophylaxis beyond day 100 in Allo-HSCT is currently under way (ClinicalTrials.gov Identifier: NCT03930615).

Immune Reconstitution After Allo-HSCT

Following Allo-HSCT, neutrophils are usually the first cell line to reconstitute within 2–3 weeks, followed by natural killer (NK) cells and T cells by day 100. The deficiency in cellular immunity increases the risk of reactivation of viral infections. Humoral immunity can take 1–2 years to reconstitute.

CMV-specific CD4+ and CD8+ T helper cells play an important role in controlling CMV reactivation. They produce various cytokines such as interferon γ, IL-2, and TNF α, at different stages of maturation which likely contributes to controlling the CMV infection [45–47]. The absence of CMV-specific T cell response has been associated with late CMV disease and death [48]. In a study by Hakki et al., low absolute CD4 and CD8 T cells at 3 months were associated with delayed development of CMV-specific T cell immunity [49]*. The presence of CMV-specific T cells has been shown to be protective against the development of CMV disease and also helps with faster recovery [49–52]. The various factors that have shown to delay the development of immune reconstitution are the type of conditioning regimen, use of steroids, GVHD, HLA-mismatched or unrelated donor transplants, bone marrow as the source of stem cells, and use of ganciclovir prophylaxis [49, 50, 53]. There are new and emerging treatments

for GVHD like ruxolitinib which may affect T cell function and further delay immune reconstitution.

CMV Cell-Mediated Immunity Assays

CMV-specific immunity assays measure the cytokines that are produced by CD4+ and CD8+ T cells by various methods as listed in Table 1. These studies have shown that the tests correlate well with the development of immunity and hence predict progression to CMV disease [54–63]. The measurement of CMV cell-mediated immunity (CMI) has a promising potential to assist with risk stratification of patients and also to develop an individualized prevention strategy for each patient. It may help in determining the duration of prophylaxis and treatment, thereby minimizing drug exposure.

The net state of immunosuppression after HSCT is affected by various factors such as GVHD, different immunosuppressive drugs used for GVHD, cancer relapse, and the conditioning regimen. Hence, measuring the CMV-CMI at single time point may not be an accurate surrogate measure of immune reconstitution. Longer term monitoring may be needed, especially in patients with ongoing immunosuppression. The optimal frequency of testing also remains to be determined. These tests have several important limitations—lack of standardization and high costs. In Figure 1, we propose an algorithm to use CMV-CMI assay for monitoring in Allo-HSCT patients.

CMV Treatment

Ganciclovir and Valganciclovir

Ganciclovir (GCV) is converted in vivo to triphosphate form and inhibits replication of CMV DNA. The drug is available in intravenous and oral formulations, although the oral formulation is limited by poor bioavailability. Valganciclovir (VGCV) is an oral prodrug of ganciclovir. A randomized open label trial comparing valganciclovir with intravenous (IV) ganciclovir showed non-inferiority in efficacy, with no difference in toxicities [64]. Another study showed the absolute bioavailability was significantly higher with oral valganciclovir compared to IV ganciclovir, even in patients with grade I–II intestinal GVHD [65]. VGCV showed similar efficacy as ganciclovir in reducing CMV viral load in patients with T cell depleted allografts [66].

Foscarnet

Foscarnet is a pyrophosphate analog and acts by selectively inhibiting viral polymerase, and is available only in intravenous formulation. A randomized, controlled, multi-center trial that compared ganciclovir and foscarnet showed similar efficacy and survival at 180 days, with less hematotoxicity in the foscarnet arm [67]. It maybe preferred choice for preemptive therapy when marrow toxicity is a concern, especially in the pre-engraftment phase and in cases of ganciclovir resistance. Foscarnet can cause nephrotoxicity by causing direct damage to the renal tubular cells, electrolyte imbalances especially potassium and magnesium, which require very close monitoring. It should be avoided in patients with or at risk of renal disease.

Table 1. CMV cell-mediated immunity assays and published studies

Name of assay/test	Mechanism	Study	Results
ELISPOT CMV	Measurement of IFN γ by ex vivo stimulation of CD4+ and CD8+ T cells by CMV antigens, which causes the cells to release it	Prospective multi-center observational study of 241 CMV+ allogenic SCT [54]	Low CMV-CMI was significantly associated with clinically significant CMV infection, compared to the patients who had high CMI (RR 5.3, 95% CI 2–14) Low CMV-CMI and clinically significant CMV infection were associated with highest all-cause mortality
		Prospective observational cohort study of 55 CMV + HCT recipients [55]	Patients with low CMV-CMI were 8.3 times more likely to progress to clinically significant CMV infection Sensitivity of 94% in predicting CMV disease progression
		Prospective observational cohort study of 63 CMV + Allo-SCT recipients [56]	CMV-specific immune response was significant in preventing CMV reactivation Sensitivity of 91% and NPV 88%
Quantiferon CMV assay	HLA restricted CMV epitopes are used to stimulate CD 8+ T cells. It is used with positive and negative control. ELISA is used to measure IFN γ produced by the T cells	Prospective study of 41 allogenic SCT patients [57]	Incidence of CMV reactivation was higher in patients who did not reconstitute CMV-specific immunity (65%) compared with those who did (27%). The peak viral loads were also higher in patients who did not reconstitute CMI
		Prospective study of 36 allogenic stem cell transplant patients [58]	CMV-specific reconstitution within 3 months of transplant is protective against CMV reactivation
		Prospective study of 22 allogenic SCT patients [59]	Patients with CMV-specific immunity spontaneously cleared viremia (67%) more frequently than those who did not (15%). Their CMV viral loads were also lower during reactivation.
Intracellular cytokine staining	Measurement of multiple cellular markers such as TNF α, IFN γ, and IL-2, by stimulation of CD4+ and CD8+ cells using CMV-specific peptides	Prospective multicenter open label study comparing preemptive therapy guided by CMV viral load+ CMV immunity assay vs CMV viral load alone [60]	The cumulative incidence of recurrent CMV DNAemia was significantly lower in the group monitored using CMV-CMI

Table 1. (Continued)

Name of assay/test	Mechanism	Study	Results
Tetramer staining	Tetramers are major histocompatibility complexes that are used to detect antigen-specific T cells	Prospective study of 114 patients who underwent SCT, monitoring for 2 years [61]	The presence of CMV-specific T cell immunity before D +50 was protective against recurrent CMV reactivation
		Prospective tri-center study of 278 patients who underwent SCT [62]	Reconstitution of CMV-specific immunity leads between D +50 and D +75 in D+/R+ HCT recipients was protective against CMV reactivation

Abbreviations: *CMV*, cytomegalovirus; *IFN*, interferon; *SCT*, stem cell transplantation; *CMI*, cell-mediated immunity, *NPV*, negative predictive value, *ELISA*, enzyme-linked immunosorbent assay; *TNF*, tumor necrosis factor; *IL*, interleukin

Maribavir

Maribavir is a benzimidazole antiviral drug that acts by inhibiting viral protein kinase UL 97, thereby inhibiting viral replication. In a phase 2 trial of Allo-HSCT and solid organ transplant patients that compared different doses of maribavir with valganciclovir, there were similar response rates (79% vs 67%) at 6 months. There was a higher incidence of GI side effects (especially dysgeusia) that led to drug discontinuation in the maribavir group (23%). However, the incidence of neutropenia was much lower compared to valganciclovir (6% vs 22%) [68•]. In a phase 2 randomized controlled trial of maribavir at different doses for refractory and resistant CMV infections, undetectable CMV viral load was achieved in 6 weeks in 63–70% patients. However, recurrent infections occurred in 25 (20%) patients, of which 13 developed resistance mutations to maribavir [69]. None of these studies reported any significant marrow or renal toxicity associated with maribavir. These studies have shown that maribavir is a promising oral drug for preemptive therapy and treatment of resistant viral infections without marrow toxic effects, although its long-term use may be limited by the potential development of drug resistance.

Cidofovir

Cidofovir is a nucleotide analog that is phosphorylated to its diphosphate form and inhibits viral DNA polymerase. It is available in IV formulation and is typically administered once weekly. Its use is limited due to significant risk of nephrotoxicity by causing tubular damage. This can be reduced by administering it with saline and probenecid which decreases its renal excretion. It can also cause bone marrow suppression and ocular side effects. Several studies have reported ocular side effects such as uveitis, iritis, and hypotonia, especially in patients who received cidofovir for treatment of CMV retinitis. It was observed with both intravitreal and intravenous formulations [70]. Its use can be considered in management of resistant CMV infections, if no other drug options are available.

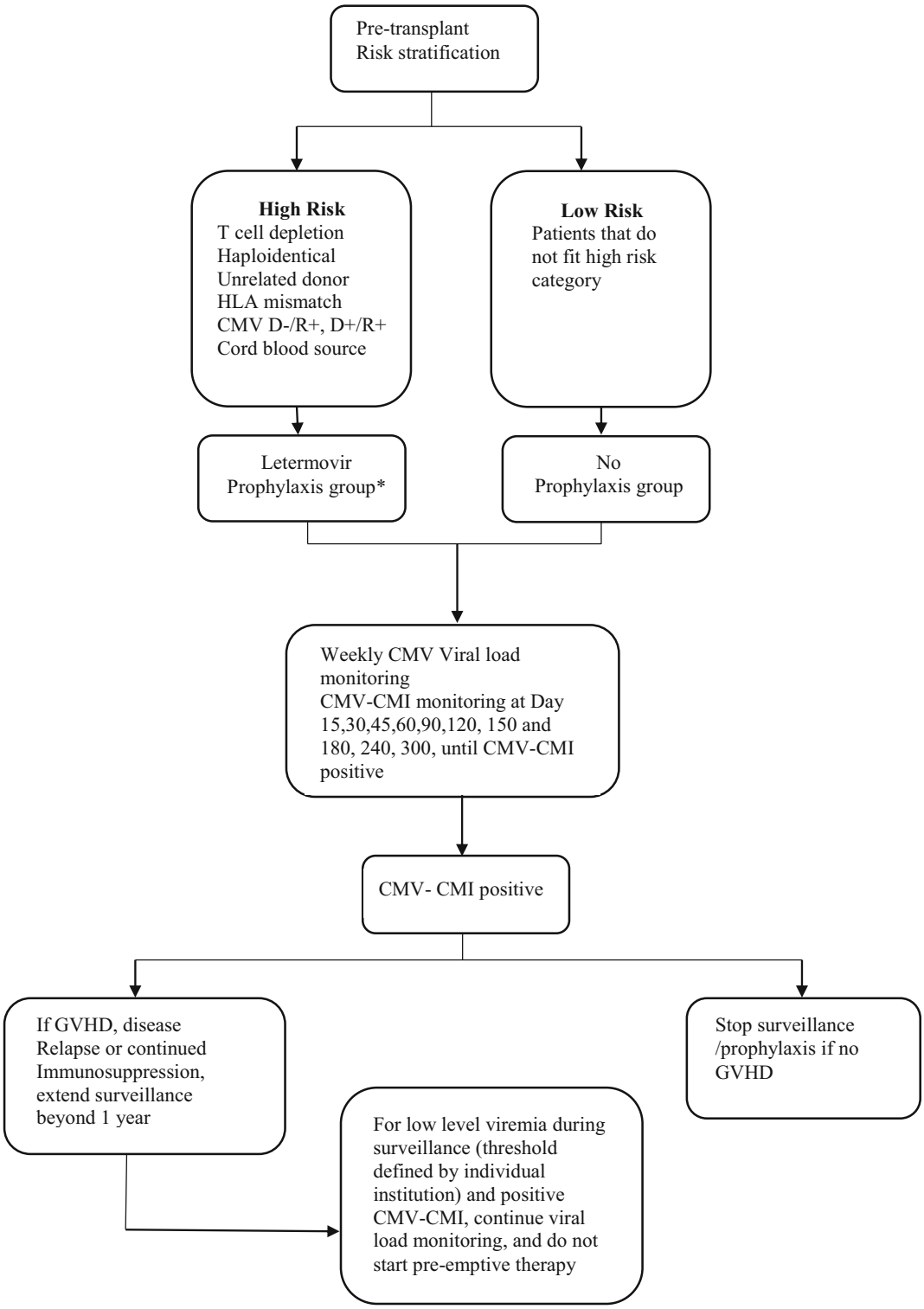

Fig. 1. Proposed algorithm for implementation of CMV-CMI assays for monitoring and interventions.

Brincidofovir

Brincidofovir (CMX001) is an oral lipid conjugate prodrug of cidofovir, which reduces the nephrotoxic and marrow toxic side effects of IV cidofovir. A phase 3 randomized controlled trial that compared brincidofovir to placebo for CMV prophylaxis in Allo-HSCT patients failed to show a reduction in clinically significant CMV infections at 24 weeks. The drug was also associated with increased rates of diarrhea and GVHD [38], and so its use was never FDA approved for this indication.

Currently, valganciclovir and ganciclovir are the preferred and first-line agents for treatment of CMV viremia and infection. However, bone marrow suppression is a major limitation of these drugs. We prefer to use foscarnet for treatment for early CMV reactivation during the pre-engraftment phase in order to prevent marrow toxicity associated with valganciclovir and ganciclovir. We usually treat for at least 2 weeks or until the CMV viremia clears, whichever is longer [71••]. We have described a proposed algorithm for management of CMV viremia in Figure 2.

CMV Antiviral Drug Resistance

Refractory CMV infection is defined as rising CMV viral load (>1 log) despite being on appropriately dosed therapy for 2 weeks; resistant CMV infection is defined as refractory viremia with identification of genotypic drug resistance mutations [72]. The prevalence of CMV drug resistance mutations has been reported ranging from 0 to 8% in Allo-HSCT patients [73–75]. One study reported a resistance rate of 14% in haploidentical HSCT patients who had been on prolonged antiviral treatment (median = 70 days) [76]. The failure to control CMV in HSCT population is more often due to immunologic failure than drug resistance. Mutations in the UL97 kinase gene confer resistance to ganciclovir, valganciclovir, and maribavir. In patients with UL97 kinase mutations that have less than 5-fold GCV resistance and no end-organ disease, ganciclovir at increased dose of 7.5–10mg/kg can be used. For mutations that confer greater than 5-fold resistance, foscarnet monotherapy is recommended. Mutations in the UL54 gene affects the viral DNA polymerase enzyme and can cause resistance to foscarnet and cidofovir in addition to ganciclovir, valganciclovir, and maribavir. The drug of choice for treatment in this case would depend on the resistance pattern [73]. UL97 gene mutations are more common in HSCT than UL54 gene mutations.

Adoptive T Cell Therapy

Since cell-mediated immunity is essential for control of refractory viral infections, the use of T cells is an attractive emerging therapy. It can be useful in controlling resistant and refractory CMV infections. There are various ways to generate virus-specific T cells, which involves stimulation of virus-specific cells by using a viral protein. These cells can be used in vivo for further expansion or used for direct infusion in the recipient [77]. T cells can be obtained from a CMV seropositive matched donor by using various isolation methods like HLA class multimers and interferon γ capture. The process of obtaining these cells from the donors can take 4–6 weeks, which makes this procedure impractical for rapid treatment of severe CMV disease. However, third party donors are now

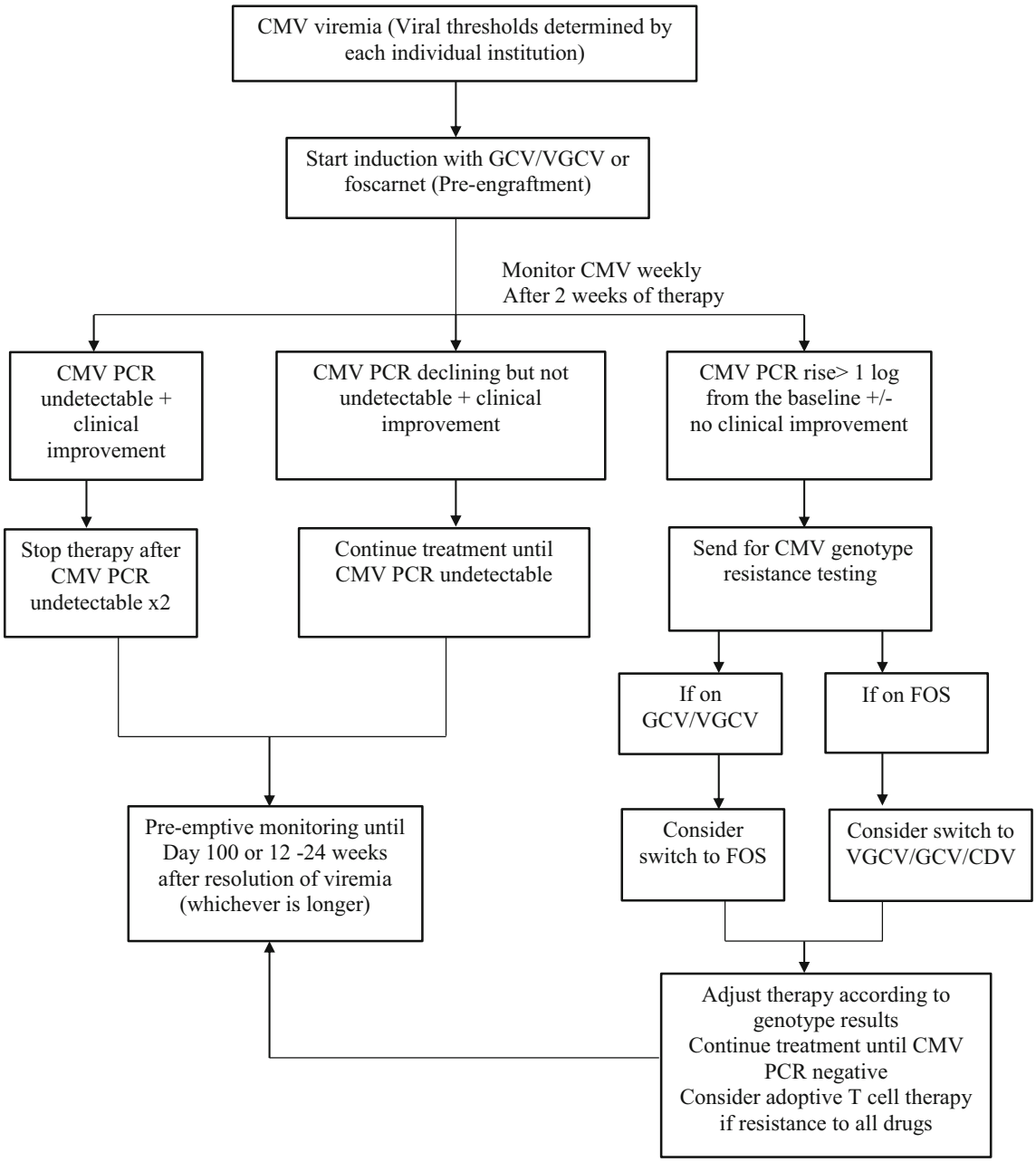

Fig. 2. Proposed algorithm for management of CMV infection in stem cell transplant population.

being used to create banks for off-the-shelf products for immediate use [78]. There is a theoretical concern about graft versus host disease due to HLA mismatches from third party products; however, the reported rate has been low so far in published studies [79–84]. Table 2 lists the various studies over the past 5 years that used adoptive T cells for treatment of refractory CMV infections. These studies were limited by small numbers and lacked comparison

Table 2. Clinical trials of adoptive T cell therapy for CMV infection in SCT population over last 5 years

Study	Source of T cells	Description	Outcomes
Tzannou et al. 2016 [79]	Third party	17 Allo-SCT patients with persistent CMV	Response rate of 94% by week 6. Nine patients had concomitant rise in CMV-specific T cells
Withers et al. 2017 [80]	Third party donors by in vitro stimulation	28 Allo-SCT with persistent/refractory CMV infections got partially matched 3rd party donor cells	Complete virological response was 76%. Rise in CMV-specific T cell immunity. 2 patients developed GVHD.
Neuenhahn et al. 2017 [81]	8—stem cell donor 8—3rd party donor	Allo-SCT patients with refractory CMV infection and lacking virus-specific T cells were treated with a single dose of ex vivo major histocompatibility complex-Streptamer-isolated CMV epitope-specific donor T cells.	Complete and partial virological response rates were 62.5% and 25%, respectively.
Pei et al. 2017 [82]	CMV seropositive donors, by in vitro stimulation	32 haplo-SCT patients with refractory CMV infection	27 of 32 patients cleared CMV in 4 weeks. There was an improvement in cytokine production and proliferation of CMV-specific T cells. These were not restored in the 5 patients who did not clear CMV.
Abraham et al. 2019 [83]	Cord blood derived	virus-specific T cells	14 Allo-SCT patients who received cells for prophylaxis and infection.
7 patients who received	prophylaxis did not develop reactivation. Out of 4 patients who received it for CMV viremia, 1 developed CMV retinitis. 3 out of 4 had resolution, two received antiviral therapy		

Abbreviations: *CMV*, cytomegalovirus; *SCT*, stem cell transplantation; *GVHD*, graft versus host disease

groups in the setting of randomized controlled trials. Additional large-scale studies are needed to assess its efficacy and side effects.

Use of Adoptive T Cell Therapy as Prophylaxis

Studies have shown that adoptive T cell therapy may also be beneficial to prevent CMV infections. In one study, 50 patients received CMV T cell infusion

28 days post-transplant compared to controls, 26 developed CMV reactivation, 5 of those were after the infusion. Nine required therapy with antivirals. The percentage of patients who required antiviral therapy was lower (17% vs 36%, p=0.01) in the treated group. There was no increase in GVHD, and overall survival was similar in both groups [84].

CMV Vaccines

Several vaccine trials for prevention of CMV infection are currently underway. Transvax (developed by Vical) is a vaccine that contains plasmids that encode pp-65 and glycoprotein B (gB). It stimulates antibody and T cell responses to both the proteins. A phase 2 randomized double-blind trial did not show a significant reduction in use of CMV antiviral therapy, but CMV viremia was lower in the vaccine group [85]. Another vaccine developed by Novartis that contains gB with M-59 adjuvant has been studied in a phase 2 trial in solid organ transplant patients. gB antibody titers increased significantly after vaccination, and inversely correlated with duration of CMV viremia [86]. PepVax (developed by Helocyte) is a chimeric peptide vaccine that contains HLA-restricted CD8 T cell epitope from pp65 protein and a Toll-like receptor 9 agonist as an adjuvant. It augments cellular immunity. A phase 1 trial showed a decrease in CMV reactivation and use of antivirals and a 2-fold increase in CD 8+ T cell immunity [87]. The results from the phase 1 trial are very promising, and a phase 2 trial is now underway. Triplex is another viral vector (Ankara) based vaccine that has shown safety and tolerability in phase 1 trial [88]. CMV vaccine development is promising, but it appears that translation to a clinical setting may take several years.

Conclusions

There remains an urgent need for better strategies and drugs for prevention and treatment of CMV infections, since it increases mortality and morbidity and risk of GVHD in Allo-HSCT patients. Prospective interventional studies are needed to further assess the utility of CMV-CMI assays. The role of extended prophylaxis with letermovir beyond day 100 is being studied in a prospective trial. Maribavir is a new antiviral drug with promising results in recent trials as preemptive therapy and treatment of resistant infections. Adoptive T cell therapy is another emerging option for treatment of resistant CMV infections; larger randomized trials are needed.

Declarations

Conflict of Interest

Niyati Jakharia declares that she has no conflict of interest. Dianna Howard declares that she has no conflict of interest. David J. Riedel declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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