Cytomegalovirus

By Maressa Santarossa, Pharm.D., BCPS, BCIDP

Reviewed by Frank P. Tverdek, Pharm.D., BCPS-AQ ID, CMQ; and Lydia D'Agostino, Pharm.D., BCPS, BCIDP

LEARNING OBJECTIVES

1. Evaluate patients for pathogenesis and risk factors associated with cytomegalovirus (CMV) infection.
2. Develop plans for prophylaxis and preemptive therapy against CMV after solid organ transplant and hematopoietic stem cell transplant.
3. Design comprehensive treatment plans for patients with CMV infection and disease.
4. Develop a plan to detect and manage CMV treatment-related adverse effects and toxicities.

ABBREVIATIONS IN THIS CHAPTER

CMV	Cytomegalovirus
DNAemia	Presence of DNA material in a sample
QNAT	Quantitative nucleic acid amplification testing
D +, D −	Organ donor CMV seropositive, seronegative
GVHD	Graft versus host disease
HSCT	Hematopoietic stem cell transplant
R+, R −	Organ recipient seropositive, seronegative
SOT	Solid organ transplantation

Table of other common abbreviations.

INTRODUCTION

Epidemiology of CMV

Cytomegalovirus (CMV) is a herpesvirus that is quite ubiquitous among adults, with seropositivity rates of about 50% in the United States (Bate 2010). In healthy adults, CMV commonly causes little to no appreciable illness; however, this virus can cause significant morbidity and mortality in immunocompromised patients, such as solid organ transplantation (SOT) and hematopoietic stem cell transplant (HSCT) recipients and individuals with AIDS or other immune disorders. In addition, CMV can cause morbidity, including hearing loss and brain damage for infants with congenital CMV. This infection is also relatively common in the immunocompetent critically ill population (Li 2018; Kalil 2009).

The seroprevalence of CMV varies among age groups, racial groups, and even income and education levels (Bate 2010). In the SOT population, CMV occurs most often in the first 3 months after SOT if no standard prophylaxis regimens are initiated, but onset is delayed if antiviral prophylaxis is administered (Razonable 2019). In the HSCT population, the infection timeline is similar as well as the delayed onset with use of antiviral prophylaxis.

Burden of CMV in SOT and HSCT Recipients

Both CMV infection and disease in the HSCT population are associated with GVHD as well as increased morbidity and mortality. Mortality from CMV is as high as 60% in the HSCT population and is often highest in patients with CMV pneumonia (Boeckh 2003). In addition, CMV has been independently associated with secondary bacterial and invasive fungal infections, graft rejection, and other complications, including Epstein-Barr virus and post-transplant lymphoproliferative disorders in the SOT population. The immunomodulatory effects of CMV are postulated to contribute to its high morbidity and mortality (Boeckh 2003; Nichols 2002).

RISK FACTORS FOR AND PATHOGENESIS OF CMV

Viral Replication and Pathogenesis

Cytomegalovirus is similar to many other human herpesviruses in that it lies dormant and can reactivate at times of stress, immunosuppression, and other illnesses. In a variety of cells, such as macrophages, fibroblasts, and endothelial cells, CMV can remain latent. T cell-specific immunity is extremely helpful in controlling the resurgence of CMV infection; therefore, most healthy adults have little to no appreciable illness when infection reactivates. Both CD4$^+$ and CD8$^+$ T lymphocytes mediate T cell immunity, and humoral immunity also plays a role in establishing latent CMV (Riddell 1995). However, immunocompromised hosts such as SOT and HSCT recipients can experience a wide array of severe clinical syndromes caused by CMV, specifically pneumonitis, retinitis, colitis, and other end-organ diseases. In patients who do not receive prophylaxis against CMV, most infections typically occur within the first 1–6 months post-SOT. However, this timeline may shift when patients receive prophylaxis such that infection is seen in the post-prophylaxis period, considered late-onset CMV (Fishman 2017). In the HSCT population, early onset CMV is typically seen within the first 100 days post-transplant (Ljungman 2010). In patients who receive prevention strategies, this timeline also typically shifts to result in late onset CMV, which occurs after day 100 post-transplant.

Risk Factors in SOT

Solid-organ transplant recipients are at an increased risk of CMV infection and disease for several reasons. First, immunosuppressive agents that are designed to deplete or eliminate T cells are known risk factors for CMV. These agents include both those commonly administered around the time of transplantation (*induction immunosuppression*) as well as agents taken for the remainder of the recipient's life (*maintenance immunosuppression*). A common induction immunosuppressant, antithymocyte globulin, blocks T cell membrane proteins, leading to inactivation and depletion of T cells (Enderby 2015). Conversely, another common induction immunosuppressant, basiliximab, affects T cell proliferation and differentiation but does not cause T cell depletion. Alemtuzumab, an anti-CD52 monoclonal antibody, results in depletion of many cell lines, including lymphocytes and macrophages (Mikulska 2018). Calcineurin inhibitors are the main agents within the maintenance immunosuppression category and include tacrolimus and cyclosporine. These agents ultimately also result in decreased proliferation of T cells. In contrast, mammalian target of rapamycin inhibitors such as sirolimus and everolimus have been shown to decrease the incidence of CMV (Razonable 2019). This effect may result from the inhibition of certain cell signaling pathways used for viral protein synthesis (Ljungman 2010).

A recent systematic review of renal transplant recipients found that age and D+/R− CMV serostatus are risk factors consistently associated with CMV infection and disease (Raval 2020). Seronegative recipients (R−) who receive an organ from a seropositive donor (D+) are at the highest risk of acquiring CMV based on the recipient's lack of preexisting viral immunity and the presence of the virus in the transplanted organ cells in the setting of immunosuppression and T cell dysfunction. The next highest risk category is D+/R+, followed by D−/R+, and then D−/R−. The risk of CMV is not uniform among different types of SOT. Lung and small bowel transplant recipients are at the highest risk compared with heart, liver, kidney, and pancreas transplant recipients. Allograft rejection is also a risk factor for CMV, especially when high-dose steroids or T cell-depleting immunosuppressants are used to treat allograft rejection.

Risk Factors in HSCT

Donor and recipient serostatus are similarly important for CMV risk stratification in HSCT recipients as with SOT recipients. However, the actual risk stratification is reversed. In the HSCT population, R+ patients with a D− donor are at the highest risk of CMV infection and disease, followed by D+/R+, then D+/R−, and then D−/R−. This risk stratification is based on the fact that CMV is still present in the recipient's cells in

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a dormant state; however, their immune system—and therefore CMV T-cell immunity—is obliterated at the time of HSCT because of conditioning chemotherapy. Many conditioning regimens are used in HSCT recipients, both myeloablative and nonmyeloablative. Some common chemotherapeutic conditioning agents include total body irradiation, fludarabine, busulfan, cyclophosphamide, and melphalan, often administered in various two- or three–drug combinations. The graft immune system (and lack of CMV T cell immunity) is then transplanted into the recipient, and the recipient is at risk of CMV reactivation with no preexisting immunity against the virus.

Other risk factors for CMV in the HSCT population include strategies aimed at minimizing GVHD: T-cell depletive therapy and myeloablative conditioning regimens (e.g., alemtuzumab), especially occurring in patients with unrelated donors or donors mismatched for ≥1 human leukocyte antigens. In addition, patients treated with high-dose steroids or other therapies for GVHD that impair T cells are at increased risk of CMV reactivation compared with those without GVHD (Ljungman 2006).

PROPHYLAXIS AND PREEMPTIVE THERAPY AGAINST CMV

SOT Prophylaxis vs. Preemptive Therapy

The two main strategies for prevention of CMV infection and disease are universal prophylaxis and preemptive therapy. Universal prophylaxis involves administering an antiviral agent to all SOT recipients routinely after transplant. Preemptive therapy involves administering no standard prophylaxis, monitoring SOT recipients for the presence of CMV DNAemia, and then administering CMV treatment promptly if DNAemia occurs. Both universal prophylaxis and preemptive therapy have several advantages and disadvantages, and the decision can be based on both hospital- and patient-specific factors. Some advantages of universal prophylaxis include decreased incidence of CMV infection and disease, which in turn may lead to decreases in rejection and certain infections. A meta-analysis also noted that universal prophylaxis reduced bacterial and fungal infections as well as death (Kalil 2005). Also, in a randomized controlled trial of valganciclovir prophylaxis versus preemptive therapy in R+ renal transplant recipients, prophylaxis was associated with significantly fewer cases of CMV infection overall compared with preemptive therapy (11% vs. 38.7%, p<0.0001) (Witzke 2012). Another similar randomized trial demonstrated that prophylaxis with oral ganciclovir significantly increased graft survival at 4 years post-transplant compared with preemptive therapy (92.2% vs. 78.3%, p=0.0425) (Kliem 2008). Some disadvantages of universal prophylaxis include medication cost, potential for medication adverse effects, and potential for patients to be nonadherent or to self-administer the prophylaxis incorrectly. Because suboptimal doses or lack of adherence to

prophylaxis may lead to CMV drug resistance, patient adherence and understanding of the importance of proper administration is essential. This point has been demonstrated by a trial exploring lower dose valganciclovir prophylaxis (450 mg/day) compared with the standard dosing of 900 mg/day (Stevens 2015). In addition, after prophylaxis is complete the risk of late onset CMV infection/disease is increased. Preemptive therapy must involve close follow-up of patients and the ability to obtain CMV QNAT values often. Potential risks of preemptive therapy include loss to follow-up and delayed CMV QNAT results. Box 1 and Box 2 summarize the advantages and disadvantages for both universal prophylaxis and preemptive therapy. In addition, the differences between these two strategies are further discussed in the American Society of Transplantation Infectious Diseases Community of Practice Guidelines (Razonable 2019).

Preemptive therapy can be used safely in kidney, liver, pancreas, and heart transplant patients who are seropositive (R+) and at lower risk. In the most high-risk category (D+/R−), preemptive therapy is only recommended in liver, pancreas and kidney transplant recipients. Lung, heart, and small bowel

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Box 1. Universal Prophylaxis for CMV: Advantages and Disadvantages

Advantages
- Efficacy—prevents both CMV infection and disease
- More data, especially in higher risk populations
- May be more feasible for patients; potentially less frequent laboratory monitoring
- Reduced mortality for CMV disease

Disadvantages
- Higher drug cost
- Risk of late-onset CMV
- Risk of adverse drug effects
- Potential development of resistance

CMV = cytomegalovirus.

Box 2. Preemptive Monitoring for CMV: Advantages and Disadvantages

Advantages
- Lower risk of drug resistance
- Lower risk of late-onset CMV
- May be more feasible, especially for patients with high pill burden or high drug costs

Disadvantages
- Intense laboratory monitoring
- Fewer data available, especially in higher risk populations
- No data demonstrating decreased mortality for CMV disease
- No prevention of CMV infection

CMV = cytomegalovirus.

transplant recipients are overall at a higher risk of CMV infection and disease; therefore, preemptive therapy is not recommended for lung transplant recipients of any serologic risk category and is less preferred for small bowel and high-risk (D+/R−) heart recipients (Razonable 2019). Preemptive therapy should involve CMV QNAT screening once weekly for at least 12 weeks post-transplant. The optimal threshold value for beginning CMV-directed therapy during preemptive therapy is still unknown. A recent randomized trial in CMV D+/R− liver transplant recipients that compared preemptive therapy with weekly CMV QNAT monitoring and valganciclovir 900 mg twice daily with prophylactic valganciclovir 900 mg once daily, both for 100 days (Singh 2020). The primary end point of this study was incidence of CMV disease at 1 year, which was significantly lower in the preemptive therapy arm versus prophylaxis arm (9% vs. 19%; p=0.04). No significant difference was noted in secondary outcomes such as mortality, infection, or graft rejection. Of interest, an increase in T cell response and neutralizing antibodies was observed in the preemptive therapy group. However, no causative conclusions can be drawn from that specific end point. Currently at most transplant centers, universal prophylaxis is the standard of care protocol. However, new compelling data such as in this recent trial may shift more protocols away from universal prophylaxis and toward preemptive therapy.

Agent Selection

Valganciclovir is typically the agent of choice for CMV universal prophylaxis, primarily because many of the other CMV antiviral agents have severe toxicities and are only available as intravenous formulations. Valganciclovir currently has FDA approval only for prevention of CMV in high-risk kidney, heart, and kidney/pancreas recipients. Of note, valganciclovir was compared with oral ganciclovir in a double-blind, double-dummy study in which the efficacy of CMV infection and disease prevention was similar for all patients except for liver transplant recipients. In liver transplant recipients, the incidence of CMV disease was significantly higher in the valganciclovir versus ganciclovir group (Paya 2004). The reason for this finding is unclear, yet some theories are altered valganciclovir metabolism, delayed seroconversion to immunoglobulin G positivity, and blunted CMV-specific T cell responses (Shiley 2009). Despite this limitation, however, valganciclovir is often used off-label for prophylaxis in liver and lung transplant recipients, and it is still recommended as the drug of choice for CMV prophylaxis according to the American Society of Transplantation Infectious Diseases Community of Practice Guidelines (Razonable 2019).

For universal prophylaxis against CMV, the typical dose of valganciclovir is 900 mg orally once daily. Some transplant centers may use an alternative dosing scheme of 450 mg orally twice daily based on the thought that this dosing strategy may result in fewer cases of neutropenia, but this dosing is not currently approved and lacks supporting clinical evidence. Low-dose valganciclovir (e.g., 450 mg/day orally for patients with normal renal function) is sometimes administered because of issues with tolerability or dose-limiting adverse effects. This dosing strategy lacks robust clinical data to support its efficacy, especially in the higher risk (D+/R−) categories (Stevens 2015). Similar outcomes have been observed compared with standard doses in intermediate-risk kidney transplant recipients (D−/R+, D+/R+); however, these data are retrospective and concerns such as development of resistance remain unknown (Kotton 2018).

High-dose valacyclovir can be used for CMV prophylaxis in renal transplant recipients in all CMV risk categories. Valacyclovir at a higher dose of 2 g four times daily results in concentrations sufficient to inhibit certain strains of CMV (Perry 1996; Cole 1987). This regimen was compared against valganciclovir prophylaxis in a randomized open-label trial, 2VAL (Reischig 2015). This study compared valacyclovir 2 g four times daily with valganciclovir 900 mg/day in renal transplant recipients with moderate or high CMV risk categories (D+/R−, D+/R+, D−/R+), and demonstrated similar efficacy in the primary end point of CMV DNAemia (43% vs. 31%, p=0.36). However, another primary end point, biopsy-proven acute rejection, was more common in the valacyclovir versus valganciclovir cohort (31% vs. 17%, p=0.03). The high valacyclovir dose of 2 g orally four times daily may lead to a risk of decreased patient adherence in response to a high pill burden and the potential for neurotoxic adverse effects. An increase in neurotoxic adverse effects was not observed in this trial; although hallucinations/confusion were numerically more common with valacyclovir versus valganciclovir (22% vs. 15%; p=0.45).

Letermovir is another agent under investigation for CMV prophylaxis. A randomized controlled trial is currently under way to compare letermovir and valganciclovir for CMV prophylaxis in kidney transplant recipients. The data are pending, however, and letermovir has not yet received FDA approval for this indication.

Duration Based on Organ Type

Duration of CMV prophylaxis is dependent on organ transplant type and on donor and recipient serostatus, as well as other patient-specific factors. Typically, organ types with a higher incidence of CMV infection and disease receive prophylaxis for longer durations, together with D+/R− transplants (Palmer 2010; Humar 2010). Other patient factors that could either shorten or lengthen duration of prophylaxis include intolerance to prophylaxis regimen (e.g., refractory neutropenia with valganciclovir), inability to afford the prophylaxis regimen, and the treatment of graft rejection. Table 1 lists some suggested durations of prophylaxis according to the American Society of Transplantation Infectious Diseases Community of Practice Guidelines. Transplant centers typically develop their own specific hospital-wide protocol for prophylaxis regimens, duration of prophylaxis, and monitoring guidelines.

Table 1. CMV Prophylaxis Durations Post-transplant

Organ	Serostatus	Duration (months)
Kidney	D+/R−	6
	R+	3
Kidney/Pancreas and Liver	D+/R−	3–6
	R+	3
Heart	D+/R−	3–6
	R+	3
Lung	D+/R−	6–12
	R+	6–12
Intestinal	D+/R−	6 (minimum)
	R+	3–6

CMV = cytomegalovirus.

Information from: Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients-Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019;33:e13512.

HSCT Prophylaxis vs. Preemptive Therapy

The definitions of universal prophylaxis and preemptive therapy in the HSCT population are the same as those in the SOT population. However, the antiviral agents used and the duration of prophylaxis differ between these transplant types. Although valganciclovir is typically the prophylactic agent of choice in the SOT population, it is rarely used in the HSCT population because of the potential for myelosuppression. In a randomized, double-blind trial in HSCT recipients at risk of late CMV disease, valganciclovir was compared with placebo as preemptive therapy (Boeckh 2015). Participants were randomized at a median of 97 and 98 days post-HSCT for valganciclovir and placebo, respectively. The preemptive therapy group was treated for CMV with valganciclovir or ganciclovir when CMV QNAT reached a threshold of at least 1000 copies/mL. The primary end point was a composite of death or CMV disease or other invasive infection at day 270 post-HSCT. This end point was met in 20% of patients who received valganciclovir versus 21% with placebo (p=0.86), although CMV DNAemia of at least 1000 copies/mL occurred less in the valganciclovir group versus the preemptive therapy group (11% vs. 36%, p<0.001). Although the rates of neutropenia did not significantly differ between groups, increased receipt of hematopoietic growth factors was observed in the valganciclovir cohort (25% vs. 12%, p=0.026). If using preemptive therapy for HSCT recipients, all patients should have weekly CMV PCR values monitored through day 100 post-transplant, and monitoring may be extended through day 200 in select scenarios, such as patients with GVHD, previous CMV reactivation, and certain higher risk transplant types (Ljungman 2019;

Green 2012). Similar to the SOT population, there is no universal CMV DNAemia threshold that indicates exactly when to begin treatment when using preemptive therapy. Some data suggest that initiating CMV treatment at a lower viral threshold (135–440 IU/mL) decreases treatment duration and prolonged CMV DNAemia compared with initiating therapy at a higher threshold (440 IU/mL or greater) (Tan 2015). This study was a retrospective analysis of HSCT recipients who received preemptive therapy for CMV DNAemia. Still, no consensus exists regarding the optimal level of CMV DNAemia at which to initiate antiviral therapy.

Agent Selection

Because valganciclovir is less commonly used in the HSCT population than the SOT population, other prophylaxis options are available: letermovir and (val)acyclovir. Letermovir was more recently approved for this indication and is beginning to become more widely used in certain patients who have an increased risk of developing CMV infection and/or disease. Valacyclovir has been studied in the HSCT population and is sometimes used in combination with preemptive monitoring.

Valacyclovir

Similar to the SOT population, high-dose valacyclovir has been studied for the prevention of CMV in the HSCT population. In a randomized controlled trial of R+ or D+ HSCT recipients who received intravenous acyclovir initially, participants then were randomized to either oral valacyclovir 2 g four times daily or acyclovir 800 mg four times daily through week 18 post-HSCT (Ljungman 2002). The primary end point of CMV infection/disease was noted in 40% of the acyclovir group compared with 28% of the valacyclovir group (p<0.0001); however, no significant difference in survival was noted between groups. Despite these data, valacyclovir is often used at lower doses for the prevention of herpes simplex virus and varicella zoster virus and may be combined with preemptive therapy as a CMV prevention strategy.

Letermovir

Letermovir is the newest approved CMV-active antiviral agent and is an inhibitor of the CMV viral terminase complex. It is currently indicated for the prevention of CMV infection and disease in patients with HSCT who are R+. Letermovir was studied in this population in a phase III randomized controlled trial versus placebo (Marty 2017). The results of this trial revealed that letermovir is an effective and safe option for the prevention of CMV in HSCT recipients. A key finding was that the rates of myelosuppression were comparable between groups. Myelosuppression is a major concern with using valganciclovir in this patient population and the main reason why traditionally most R+ HSCT recipients receive preemptive therapy rather than prophylaxis. In addition to a decrease in clinically significant CMV infections, patients in the letermovir group also had decreased mortality compared with

Patient Care Scenario

P.Q., a 48-year-old man, underwent an allogeneic-matched related HSCT 1 week ago (D−/R+). His medical team asks you about the best method for prevention of CMV infection/disease in this patient. What is the most appropriate recommendation for P.Q.?

ANSWER

In allogeneic HSCT recipients, it is important to note that risk of CMV infection/disease is the reverse of that for SOT recipients. Patients who are R+ are at a higher risk than those who are negative. Therefore, P.Q. is at a high risk of developing CMV infection/disease and initiation of prophylaxis is appropriate.

Several options are available for CMV prophylaxis. Valganciclovir and ganciclovir are the typical drugs of choice in the SOT population. However, because of the myelosuppressive adverse effects of ganciclovir and valganciclovir, these drugs are rarely used in the HSCT population for the prevention of CMV, especially only 1 week after transplant. Another option for CMV prevention in this population is high-dose valacyclovir, which is superior for CMV prevention compared with standard doses. However, breakthrough CMV is still often seen when using this regimen, which would be a serious concern for a patient who is high risk (D−/R+).

Letermovir is the newest prophylactic agent available, and it has been studied in allogeneic HSCT patients who are R+. Letermovir is proven to prevent CMV infection and disease compared with placebo, including patients who received acyclovir, valacyclovir or famciclovir prophylaxis. In addition, letermovir has a proven mortality benefit compared with placebo. Therefore, the best answer for this patient is to initiate letermovir prophylaxis through at least day 100 post-HSCT.

1. Ljungman P, Perez-Bercoff L, Jonsson J, et al. Risk factors for the development of cytomegalovirus disease after allogeneic stem cell transplantation. Haematologica 2006;91:78-83.
2. Ljungman P, de la Camara R, Milpied N, et al. Randomized study of valacyclovir as prophylaxis against cytomegalovirus reactivation in recipients of allogeneic bone marrow transplants. Blood 2002;99:3050-6.
3. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. N Engl J Med 2017;377:2433-44.
4. Ljungman P, Schmitt M, Marty FM, et al. A mortality analysis of letermovir prophylaxis for cytomegalovirus (CMV) in CMV-seropositive recipients of allogeneic hematopoietic cell transplantation. Clin Infect Dis 2020;70:1525-33.

the placebo group at week 24 (Ljungman 2020; Marty 2017). Letermovir is available in both intravenous and oral formulations at 480 mg once daily or 240 mg once daily when administered with cyclosporine, according to the manufacturer's package insert. Letermovir should be initiated between day 0 and 28 post-HSCT. Most adverse events reported with letermovir were comparable with placebo, and the most common adverse events were nausea, diarrhea, and vomiting. Letermovir has several drug–drug interactions because of CYP3A and organic anion-transporting polypeptide 1B1 and 1B3 inhibition. Common interacting medications include azole antifungals, anti-epileptics, rifamycins, statins, calcineurin inhibitors, warfarin, and amiodarone. A comprehensive analysis of drug–drug interactions should always be performed when initiating or discontinuing letermovir. Notably, letermovir is not active against herpes simplex virus or varicella-zoster virus. Because HSCT recipients are also at risk of herpes simplex virus and varicella zoster virus reactivation, additional prophylaxis with either acyclovir or valacyclovir must also be used.

Duration

Duration of CMV prophylaxis in patients with HSCT is typically continued through day 100 post-transplant (about 3 months). Duration of CMV prophylaxis may differ based on patient-specific factors such as GVHD, infections, and graft failure. Recent data also describe the extension of letermovir prophylaxis in a retrospective analysis of 20 patients with HSCT and GVHD who were R+ and received letermovir prophylaxis beyond day 100 post-transplant (Bansal 2020). Results indicated that only 5% of the cohort (1 patient) developed CMV infection during the extended duration prophylaxis period, which is quite effective in this high-risk population.

Investigational Vaccines

Many CMV vaccines are currently in development, but none are currently FDA approved. In addition, many categories of CMV vaccines are currently in development, including live attenuated vaccines, recombinant viral or subunit vectors, or gene-based vaccines. Several expert groups recommend that CMV vaccine development should focus on the most high-risk patient populations (D+/R− SOT patients), the impact of vaccination on seropositive patients, and an evaluation of humoral (B cell) and cellular (T cell) immunity and the duration of this immunity (Kotton 2018).

DIAGNOSIS OF CMV INFECTION AND DISEASE

CMV Infection Diagnosis

Cytomegalovirus infection is defined as isolation of the virus or viral proteins or nucleic acid in any body fluid or specimen. The term *CMV replication* can sometimes be used interchangeably with *CMV infection* (Ljungman 2017). For

example, patients with CMV DNAemia would be considered to have CMV infection, regardless of symptomatology. Presence of CMV is most commonly diagnosed by molecular methods that detect the presence of CMV DNA in bodily fluids. The preferred method is QNAT—a *quantitative* test versus a *qualitative* test. However, despite the calibration to the WHO international standard, CMV viral load values continue to vary among laboratories (Hirsch 2013). An absolute threshold for CMV DNAemia that indicates when to begin treatment is still unknown in both the SOT and HSCT populations. Therefore, it can be difficult to decide when to initiate antiviral treatment directed against CMV. Some patients may have low-level CMV DNAemia that spontaneously resolves, despite the patient being at risk of clinically significant CMV infection (Kotton 2018). Some thresholds previously studied in preemptive SOT literature range from 1500 IU/mL to almost 4000 IU/mL (Martin-Gandul 2014; Atabani 2012). Thresholds previously studied in preemptive HSCT literature tend to be lower; ranging from 100–1000 IU/mL, dependent on patient-specific risk factors (Boeckh 2009). As discussed earlier in this chapter, many critically ill patients also have a high prevalence of CMV DNAemia, despite being immunocompetent. Whether antiviral therapies are beneficial in this patient population or whether this patient population has an increased mortality remains unknown (Li 2018; Kalil 2009). The rate of increase of the CMV viral load may be more predictive of subsequent CMV disease than the level of DNAemia (Emery 2000).

CMV Disease Diagnosis

Cytomegalovirus disease is defined as a syndrome encompassing both CMV infection and associated symptoms (Ljungman 2017). Symptoms may include end-organ disease or viral symptoms such as fever, cytopenias, and malaise. Tissue-invasive CMV disease can be present in many organs, commonly the lung, GI tract, eyes, and liver. Histopathology is the gold standard for diagnosis of end-organ CMV disease. Although rare, it is possible to have CMV end-organ disease without the presence of DNAemia. Thus, it is important to obtain samples for histopathology if CMV disease is strongly suspected, regardless of the presence of DNAemia.

Cytomegalovirus pneumonia can be one of the most devastating complications of the virus. For definitive diagnosis, CMV must be isolated in the lung tissue and be coupled with clinical signs or symptoms of pneumonia, which may include hypoxia, tachypnea, dyspnea, and/or infiltrates on chest imaging (Ljungman 2017). Probable CMV pneumonia constitutes clinical pneumonia signs and symptoms, together with isolation of CMV in bronchoalveolar lavage fluid. Clinical signs and symptoms must be incorporated into the diagnosis of CMV pneumonia based on the fact that CMV can be present in the lungs as a result of viral shedding and is not always a contributor to clinical disease.

Cytomegalovirus GI disease can involve either the upper or lower (colitis) GI tract. The diagnosis of proven CMV GI disease requires GI symptoms, mucosal lesions, and CMV detected in tissue samples. Symptoms can include diarrhea, nausea, and vomiting. The diagnosis of probable CMV GI disease involves GI symptoms and CMV detected in GI tissue, but no identified mucosal lesions (Ljungman 2017).

Cytomegalovirus hepatitis does not have an established category for probable disease. Proven CMV hepatitis is diagnosed by abnormal liver function tests and CMV detected in hepatic tissue. Clinicians must also exclude other causes of hepatitis (Ljungman 2017).

Proven CMV retinitis requires an ophthalmologic examination with findings consistent with signs of CMV retinitis. If this examination is not possible, CMV retinitis can also be diagnosed by CMV detected by QNAT in the vitreous fluid of the eye (Ljungman 2017).

Cytomegalovirus encephalitis and ventriculitis must involve CNS symptoms and CMV isolation in the CNS tissue to be considered proven disease. Alternatively, probable disease would involve CNS symptoms and detection of CMV in the CSF and abnormal CNS imaging or EEG (Ljungman 2017).

Proven CMV nephritis is diagnosed by the detection of CMV in kidney tissue specimen, coupled with renal dysfunction. Kidney tissue sampling is typically performed with a kidney biopsy specimen of the allograft. Notably, CMV can be shed in the urine similar to respiratory specimens; therefore, detection of CMV in the urine is not diagnostic of disease. Similarly, CMV cystitis also requires a bladder biopsy specimen for proven disease diagnosis (Ljungman 2017).

Cytomegalovirus myocarditis requires detection in a cardiac biopsy specimen and clinical myocarditis to be considered a diagnosis of proven disease. Similarly, proven CMV pancreatitis requires detection by tissue biopsy and clinical signs of pancreatitis (Ljungman 2017).

TREATMENT OF CMV INFECTION AND DISEASE

First-Line Therapies and Alternatives

Ganciclovir/Valganciclovir

Ganciclovir and valganciclovir are first-line therapies for CMV infection and disease and both inhibit CMV DNA polymerase. Valganciclovir is the prodrug compound of ganciclovir, and it has greater bioavailability compared with oral ganciclovir. Because of bioavailability issues, oral ganciclovir is no longer routinely used for the treatment of CMV. Ganciclovir is dosed at 5 mg/kg intravenous every 12 hours initially and then transitioned to 5 mg/kg/day intravenously thereafter. Valganciclovir is dosed at 900 mg every 12 hours initially and then transitioned to 900 mg/day thereafter. Both medications must be adjusted for renal dysfunction (Table 2). Both ganciclovir and valganciclovir can cause significant reversible myelosuppressive toxicity, which may manifest as neutropenia, leukopenia, anemia, thrombocytopenia, and/or pancytopenia. These toxicities can be severe and warrant frequent

Table 2. Renal Dosage Adjustments for Ganciclovir and Valganciclovir

Creatinine clearance (mL/min)	Ganciclovir induction dose	Ganciclovir maintenance dose
≥ 70	5 mg/kg every 12 hr	5 mg/kg every 24 hr
50−69	2.5 mg/kg every 12 hr	2.5 mg/kg every 24 hr
25−49	2.5 mg/kg every 24 hr	1.25 mg/kg every 24 hr
10−24	1.25 mg/kg every 24 hr	0.625 mg/kg every 24 hr
< 10/HD	1.25 mg/kg after HD TIW	0.625 mg/kg after HD TIW

Creatinine clearance (mL/min)	Valganciclovir induction dose	Valganciclovir maintenance dose
≥ 60	900 mg every 12 hr	900 mg every 24 hr
40−59	450 mg every 12 hr	450 mg every 24 hr
25−39	450 mg every 24 hr	450 mg every 48 hr
10−24	450 mg every 48 hr	450 mg BIW
< 10/HD	200 mg oral solution after HD TIW	100 mg oral solution after HD TIW

BIW = twice weekly; TIW = three times weekly; HD = hemodialysis.
Information from: Manufacturers' package insert.

monitoring of patients' complete blood counts and potentially the addition of hematopoietic growth factors or platelet transfusions. The timeline of myelosuppression can vary significantly among patients but it often reported to occur around 2−3 months post-SOT (Brum 2008). It is not recommended to decrease the dose of ganciclovir or valganciclovir to mitigate bone marrow suppression because this strategy may result in significant CMV resistance and/or treatment failure, according to manufacturer's package inserts.

The VICTOR trial sought to determine whether oral valganciclovir is an acceptable treatment regimen in patients with CMV disease compared with intravenous ganciclovir (Asberg 2007). In this randomized study of SOT patients, most were renal transplant recipients. This study concluded that oral valganciclovir was noninferior to intravenous ganciclovir with respect to the primary outcome of the eradication of CMV DNAemia at 21 days. The caveat to this trial for treating patients with CMV disease is that patients should have the ability to absorb oral medications adequately; therefore, those with severe colitis and/or life-threatening CMV may warrant initial intravenous ganciclovir therapy.

Foscarnet

Foscarnet is an antiviral pyrophosphate agent active against CMV. Foscarnet causes selective inhibition at the pyrophosphate binding site on CMV DNA polymerases. Unlike other CMV antiviral agents, foscarnet does not require phosphorylation by thymidine kinase to exert its antiviral activity. However, it is typically reserved for patients with suspected or confirmed resistance or intolerance to ganciclovir and severe CMV infection/disease because of the drug's significant toxicities. These effects include nephrotoxicity and electrolyte imbalances (hypocalcemia, hypophosphatemia, hyperphosphatemia, hypomagnesemia, hypokalemia), which can result in paresthesias and seizures, according to the manufacturer's package insert. Foscarnet is dosed at either 60 mg/kg intravenously every 8 hours or 90 mg/kg intravenously every 12 hours for induction, and 90−120 mg/kg/day intravenously for maintenance. Foscarnet has been dosed using these two induction-dosing strategies in clinical trials, but no trial to date has compared these two dosing strategies in the same study. However a study comparing the two maintenance dosing strategies of 90 mg/kg/day and 120 mg/kg/day in CMV retinitis patients with AIDS. This study did not show a significant difference in efficacy with regard to progression of retinitis between the two groups; however, it did show a significant difference in survival (157 vs. 336 days, p<0.001). No significant increase in toxicity was noted with the higher maintenance groups, but the sample size was small. Therefore, the maintenance dose may be selected based on patient-specific factors. To decrease the risk of nephrotoxicity, it is recommended to administer 750−1000 mL of intravenous fluids before the first infusion of foscarnet, and then between 500−1000 mL with each subsequent dose, dependent on dosing. Foscarnet must be dose adjusted for renal dysfunction (Table 3), and should be dosed using the modified Cockcroft-Gault equation shown as follows:

Modified Cockcroft-Gault equation:

$$\frac{140 - age\ (\times\ 0.85\ for\ females)}{serum\ creatinine \times 72} = mL/minute/kg$$

Table 3. Foscarnet Renal Dose Adjustments

CrCl (mL/min/kg)	CMV Induction Dosing		CMV Maintenance Dosing	
Modified Cockcroft-Gault	Equivalent to: 60 mg/kg every 8 hr	Equivalent to: 90 mg/kg every 12 hr	Equivalent to 90 mg/kg every 24 hr	Equivalent to: 120 mg/kg every 24 hr
> 1.4	60 mg/kg every 8 hr	90 mg/kg every 12 hr	90 mg/kg every 24 hr	120 mg/kg
> 1.0−1.4	45 mg/kg every 8 hr	70 mg/kg every 12 hr	70 mg/kg every 24 hr	90 mg/kg every 24 hr
> 0.8−1.0	50 mg/kg every 12 hr	50 mg/kg every 12 hr	50 mg/kg every 24 hr	65 mg/kg every 24 hr
> 0.6−0.8	40 mg/kg every 12 hr	80 mg/kg every 24 hr	80 mg/kg every 48 hr	105 mg/kg every 48 hr
> 0.5−0.6	60 mg/kg every 24 hr	60 mg/kg every 24 hr	60 mg/kg every 48 hr	80 mg/kg every 48 hr
> 0.4−0.5	50 mg/kg every 24 hr	50 mg/kg every 24 hr	50 mg/kg every 48 hr	65 mg/kg every 48 hr
< 0.4	Not recommended	Not recommended	Not recommended	Not recommended

Information from: Manufacturers' package inserts.

Cidofovir

Cidofovir is an antiviral agent that is active against CMV by inhibition of DNA polymerase. This agent is a nucleoside phosphonate analog that is incorporated into the nascent chain and then phosphorylated by intracellular kinases to reach its active form (Cundy 1999). Cidofovir metabolites possess a long intracellular half-life, which results in a long duration of antiviral activity and allows for dosing less often. (Cundy 1996, 1995). Cidofovir is recommended as alternative therapy for CMV infection/disease, given its high incidence of adverse effects. Of note, cidofovir lacks penetration into the CNS, so its use is limited for CMV encephalitis infections. Cidofovir is dosed at 5 mg/kg intravenous once weekly for 2 weeks, then every other week thereafter in patients with normal renal function, according to the manufacturer's package insert. This threshold is defined as serum creatinine (SCr) 1.5 mg/dL or less, CrCl greater than 55 mL/minute, and urine protein less than 100 mg/dL. Cidofovir is contraindicated in patients with baseline renal function that is worse than these values. Renal dose adjustments should be made for those who have an increase in SCr of 0.3−0.4 mg/dL above their baseline, and cidofovir should be discontinued in those with an increase in SCr of more than 0.4 mg/dL or significant (3+) proteinuria. Dose adjustments can be made by lowering the maintenance dose from 5 mg/kg to 3 mg/kg every other week. The administration of cidofovir can be complex because additional measures are taken to minimize renal toxicity. Beginning 3 hours before cidofovir infusion, 2 g of probenecid should be administered, and 1 g should be administered 2 hours after and 8 hours after cidofovir. In addition, patients should receive 1 L of normal saline with each cidofovir infusion over 1−2 hours before the dose. Another 1 L of saline can be given immediately after the cidofovir infusion for patients who can tolerate it. Unfortunately, cidofovir therapy is limited by a very high incidence of nephrotoxicity, including SCr elevation and proteinuria. Administration of cidofovir with concomitant probenecid and hydration decreases the incidence of nephrotoxicity while maintaining adequate drug levels in the serum. Probenecid decreases cidofovir accumulation in the kidney by inhibition of active tubular secretion, an interaction similar to other drugs (Cundy 1995). In addition, this hydration dilutes the concentration of cidofovir delivered to the kidneys. Cidofovir therapy can also result in myelosuppression, namely neutropenia; however, this effect has been mostly noted in cidofovir-treated patients with AIDS and CMV retinitis (Lalezari 1997).

Adjunctive/Investigational Therapies
Brincidofovir

Brincidofovir (CMX001) is a prodrug of cidofovir and similarly acts through the inhibition of CMV viral polymerase. Brincidofovir is not yet approved for the prevention or treatment of CMV, but it has been investigated in the HSCT population (Marty 2019). Brincidofovir is significantly less nephrotoxic than cidofovir because of its liposomal nature, which is one of the main reasons cidofovir is avoided in clinical practice. Despite the convenience of an oral option for brincidofovir, this formulation is limited by severe diarrhea. This adverse effect necessitated significant empiric treatment of GVHD in the HSCT prophylaxis trial, which in turn may have contributed to a significant mortality imbalance (15.5% with brincidofovir vs. 10.1% with placebo). Brincidofovir is currently being studied for the treatment of other viruses such as adenovirus, and it also has activity against BK virus and other herpesviruses.

Maribavir

Maribavir is an investigational agent with activity against CMV, including strains that may be resistant to existing therapies. This novel therapy inhibits the UL97 kinase in

virus-infected cells (Prichard 2009). In a study for preemptive treatment of CMV in HSCT and SOT recipients, maribavir appeared to have a similar efficacy end point compared with valganciclovir for undetectable DNAemia after 3 and 6 weeks of therapy (Maertens 2019).

Maribavir was also studied for refractory or resistant CMV infections in both HSCT and SOT patients in another randomized phase II study (Papanicolaou 2019). Maribavir appeared to be active against refractory and/or resistant CMV in this study, although some patients developed new UL97 mutations that led to maribavir resistance. In both trials, maribavir was limited by GI adverse effects, specifically dysgeusia. Currently, maribavir is also being investigated for CMV prophylaxis post-HSCT and post-liver transplant.

Letermovir

As discussed previously, letermovir is currently only indicated for the prophylaxis against CMV in R+ HSCT recipients. However, this agent is being investigated for the treatment of refractory and resistant CMV infection and disease in addition to CMV prophylaxis in the kidney transplant population. Letermovir has been used for the treatment of refractory and/or resistant CMV in few case reports and case series, for which the results are unclear (Phoompoung 2020; Kronig 2020). Letermovir has a low barrier to resistance, and limited data show its efficacy for treatment of severe CMV infection and/or disease. More data are needed to determine the role of letermovir for the treatment of CMV. Letermovir has also been used as a "stepdown" therapy option or for secondary prophylaxis in those with resistant CMV infections, and those who may be intolerant to other therapies. In a recent poster presentation, authors describe favorable outcomes for most cases of letermovir use in patients who had a viral load of less than 1000 IU/mL. However, in those who received letermovir at an initial viral load greater than 1000 IU/mL, the outcomes were unclear and included increasing CMV DNAemia while on therapy (Linder 2020).

Leflunomide

Leflunomide is an immunomodulatory agent that is often used off-label for adjunctive treatment of CMV infection/disease. Leflunomide has antiproliferative activity by the inhibition of dihydroorotate dehydrogenase, which is involved in pyrimidine synthesis, according to the manufacturer's package insert. The evidence supporting leflunomide therapy for the treatment of CMV infection and disease has been described in few case reports and series, mostly as an adjunctive therapy option (Silva 2018; Chon 2015). It appears that leflunomide was generally well tolerated and efficacious in these difficult to treat scenarios. Leflunomide should be monitored for efficacy and safety by checking levels of the active metabolite, teriflunomide. Suggested target levels are unclear, but one study used 50–80 mcg/mL (Avery 2010). Leflunomide also carries a risk of liver toxicity; therefore, liver function test monitoring is recommended. The dosing

strategies for leflunomide for the treatment of CMV are heterogeneous. Many reports have shown success with a loading dose of 100 mg/day for 5 days, followed by 20–40 mg/day thereafter (Silva 2018; Chon 2015; Avery 2010).

CMV Immune Globulin

Cytomegalovirus immune globulin (CMVIg) is an immune globulin product with high concentrations of CMV antibodies. This agent is indicated for prophylaxis against CMV in SOT recipients, namely kidney, lung, liver, pancreas, and heart transplant recipients, according to the manufacturer's package insert. A randomized trial in renal transplant recipients studied CMVIg for prophylaxis versus placebo (Snydman 1987). In this study, CMVIg reduced CMV infection and disease significantly (60% vs. 21%, p<0.01 for CMV associated syndromes). Similarly, CMVIg prophylaxis was investigated in liver transplant recipients in another randomized placebo-controlled study (Falagas 1997). In this study, CMVIg was significantly associated with a decrease in CMV disease and an increase in 1-year survival. Despite these data, CMVIg is not often used in the setting of post-SOT prophylaxis in clinical practice. Instead, this agent is often reserved as an adjunctive therapy option for severe or life-threatening CMV infection, despite limited data for this indication. This use is likely because of the high cost of this product coupled with the FDA approval of valganciclovir, which succeeds these data. In addition to these limitations, the dosing strategies for treatment of CMV infection and disease are in the literature heterogeneous. The FDA-labeled dosing for prophylaxis against CMV infection varies between type of transplant and length of time elapsed post-transplant. Kidney transplant recipients receive 150 mg/kg within 72 hours post-transplant, and then 100 mg/kg at 2, 4, 6, and 8 weeks, followed by 50 mg/kg at 12 and 16 weeks post-transplant. All other organ recipients receive 150 mg/kg within 72 hours post-transplant, and then at 2, 4, 6, and 8 weeks, followed by 100 mg/kg at 12 and 16 weeks post-transplant, according to the manufacturer's package insert. For the treatment of CMV infection and disease, studies have investigated doses of up to 150 mg/kg twice weekly, but the optimal regimen remains unclear. In an investigation of CMVIg as an adjunctive agent for the treatment of CMV disease in the HSCT population, the time to initiation of CMVIg had no effect on survival; however, this population had a high mortality overall and the sample size was small (Alexander 2010). Overall CMVIg appears to be well tolerated; however, infusion-related reactions such as fever, chills, flushing and hypotension are possible given that it is a biologic product.

Duration of Therapy and Monitoring

In general, CMV infection and disease should be treated similarly. In the SOT population, induction (full dose) treatment should be given for at least 2 weeks, until the CMV QNAT is undetectable and clinical symptoms have resolved (Razonable 2019; Sia 2000). Maintenance treatment or secondary

prophylaxis, which involves a reduced dosing strategy for 1–3 months, can be considered after the cessation of induction treatment. To date, comparative assessment of varying durations is lacking, and decisions are often made based on patient tolerance of therapy, cost, and clinical course. Secondary prophylaxis is common in clinical practice; however, it should not be routinely recommended unless patients are at a high risk of CMV infection relapse, according to the guideline recommendations (Razonable 2019). Some studies investigating the strategy of secondary prophylaxis suggest that it may be protective against CMV relapse over the course of its administration. However, no long-term benefits have been sustained after the cessation of secondary prophylaxis and no differences in outcomes such as death or graft loss have been observed (Gardiner 2017; Sullivan 2015). The decision of whether to initiate secondary prophylaxis can be based on patient-specific factors such as lymphopenia, T cell deficiency, and/or CMV-specific T cell immune monitoring (Gardiner 2018; Kumar 2017). These methods however have not been widely adopted as standard of care and warrant further investigation.

To assess the response to therapy, CMV QNAT should be monitored weekly during treatment until undetectable. Traditionally, it was advised that CMV QNAT should remain undetectable for 2 or even 3 weeks before discontinuing therapy. However, with the introduction of newer and more sensitive CMV QNAT assays, this approach is no longer necessary. In addition, signs and symptoms of CMV infection and end-organ disease should be monitored for improvement and resolution. Clinicians should also consider a reduction in immunosuppression for patients with severe or life-threatening CMV infection and disease.

Similarly, in the HSCT population, the duration of antiviral therapy for CMV infection and disease should be at least 2 weeks, until at least one undetectable CMV test (QNAT or antigen) has been confirmed (Ljungman 2019). Secondary prophylaxis therapy may also be used for patients with long-term immunosuppression (Boeckh 2009), if CMV remains detected after 2 weeks of therapy, or in patients who have slowly decreasing CMV DNAemia (Ljungman 2019).

Drug-Resistant CMV

Drug resistance in CMV remains a major issue for both SOT and HSCT recipients, and outcomes even when treated appropriately remain poor. About 5%–10% of SOT patients treated for CMV DNAemia will have confirmed resistance, and about 0%–4% of HSCT patients will have confirmed resistance (Avery 2016).

Drug-resistant CMV is formally defined as a viral genetic alteration that decreases susceptibility to at least 1 antiviral drug (Chemaly 2019). *Refractory CMV infection* is defined as CMV DNAemia that increases by more than 1 $\log_{10}$ after at least 2 weeks of antiviral therapy, dosed appropriately (Chemaly 2019; Razonable 2019). If the CMV viral load remains

the same or higher (but less than 1 $\log_{10}$) after 2 weeks of appropriate therapy, the condition is considered probable refractory CMV infection. Similarly, *refractory CMV end-organ disease* is defined as a worsening in signs and symptoms or progression to end-organ disease after at least 2 weeks of antiviral therapy, dosed appropriately. *Probable refractory CMV end-organ* disease is defined as a lack of improvement of clinical signs and symptoms after 2 weeks of proper treatment (Chemaly 2019). Resistance to CMV drugs may be one of the potential causes of refractory CMV infection and/or disease and thus should be suspected when refractory CMV infection or disease is present.

Risk factors for CMV resistance include prolonged antiviral exposure, D+/R− serostatus, breakthrough CMV infections during prophylaxis, and intensified immunosuppression (Minces 2014). Suboptimal dosing of valganciclovir or ganciclovir is also thought to be a risk factor for the development of resistant virus. Two main mutation targets can result in CMV resistance. Mutations in the UL97 kinase gene are more commonly encountered, and they affect drug phosphorylation and confer resistance to ganciclovir/valganciclovir to varying degrees. High-dose ganciclovir may be effective against UL97 mutations in certain circumstances. Mutations may also occur in the UL54 gene, which encodes CMV DNA polymerase. Therefore, UL54 mutations confer resistance to ganciclovir and likely will confer resistance to cidofovir and/or foscarnet as well. In contrast to ganciclovir, foscarnet does not require phosphorylation, and cidofovir does not require the initial phosphorylation by a viral kinase; therefore, they are typically unaffected by UL97 mutations (Lurain 2010). Resistance mutations to letermovir exist as well, although not for UL97 or UL54 because of the novel mechanism of action for this agent. Because UL56, UL51, and UL89 encode the CMV terminase complex, their mutations can confer resistance to letermovir (Chou 2018).

Treatment outcomes for resistant CMV remain poor and optimal treatment strategies are not well defined. Foscarnet therapy for resistant CMV is limited by significant nephrotoxicity and high mortality rates, as well as issues with CMV viral clearance (Avery 2016). Alternative strategies to using foscarnet monotherapy include combining ganciclovir and foscarnet at half doses (Mattes 2004; Mylonakis 2002), high-dose ganciclovir therapy (Gracia-Ahufinger 2013), and additional adjunctive therapies. Not all UL97 and UL54 mutations are equivalent. and drug susceptibility often depends on the specific codons where the mutations occur (Lurain 2010). If a UL97 mutation is detected that would confer a 5- to 10-fold increase in ganciclovir resistance, a switch to foscarnet is recommended. However, if low-grade ganciclovir resistance is found, clinicians can instead initiate a trial of high-dose ganciclovir (up to 10 mg/kg) rather than switching therapy. Cidofovir therapy may be considered when ganciclovir resistance is caused by only the UL97 mutation because cidofovir does not require initial phosphorylation by UL97 kinase,

Table 4. Suggested Management of Refractory/Resistant CMV Infection and Disease

		Severe CMV disease	Non-severe CMV disease
Increased/persistent CMV DNAemia or persistent symptoms after 2 weeks of induction ganciclovir or valganciclovir →	Send CMV genotype for UL97/UL54 resistance testing. Assess severity and other factors for lack of improvement	Switch ganciclovir/ valganciclovir to foscarnet (induction dosing)	Increase dose of ganciclovir to 10 mg/kg every 12 hours or switch to foscarnet (induction dosing)
Analyze results of CMV genotype/resistance testing and clinical response to determine final treatment plan. Consider investigational and/or adjunctive therapies.			

CMV = cytomegalovirus.

Information from: Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients-Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019;33:e13512.

Practice Points

Cytomegalovirus is a ubiquitous herpesvirus that can cause significant morbidity and mortality in immuno-compromised patients, including both SOT and HSCT patients. Several clinical pearls for the diagnosis, pro-phylaxis, and treatment of CMV infection and disease follow:

- **The two primary options for prevention of CMV infection and disease are universal prophylaxis and preemptive therapy.**
- **Valganciclovir is the most common regimen for prophylaxis in the SOT population. Letermovir is the newest regimen for prophylaxis in the HSCT population.**
- **Typically CMV is first detected by CMV QNAT in serum; additional diagnostic recommendations are recommended to determine the extent of CMV infection and/or disease.**
- **Currently four antiviral agents are recommended for the treatment of CMV infection and/or disease: valganciclovir, ganciclovir, foscarnet and cidofovir. Ganciclovir and valganciclovir are considered first-line agents.**
- **Many of the antiviral agents used for the treatment of CMV are associated with significant toxicity. Ganciclovir and valganciclovir are associated with dose-limiting myelosup-pression, and foscarnet and cidofovir are associated with dose-limiting nephrotoxicity.**
- **Several agents are under investigation for prevention and/ or treatment of CMV, including maribavir, brincidofovir, and CMV vaccinations.**
- **Adjunctive treatment options are available for CMV in se-vere or resistant cases and include CMV immune globulin, leflunomide, and letermovir.**
- **Drug-resistant CMV continues to be a significant concern for both SOT and HSCT recipients, and outcomes are poor. Alternative options for resistant CMV are foscarnet, ganciclovir/foscarnet combination at half doses, high-dose ganciclovir, and investigational or adjunctive agents.**
- **More data are necessary to optimize the prevention and treatment of CMV. In addition, antiviral drug development and vaccine development should both be prioritized.**

unlike ganciclovir does.However, cross-resistance is still pos-sible, and cidofovir remains difficult to tolerate (Lurain 2010). A suggested guide for suspected resistant CMV is shown in Table 4.

CONCLUSION

In conclusion, CMV remains one of the most common viral infections to affect immunocompromised hosts, primarily SOT and HSCT recipients. Several patient-specific factors increase the risk of CMV infection and disease, mostly those related to T cell dysfunction. This infection and disease can cause a variety of sequelae in patients; ranging from asymp-tomatic DNAemia to end-organ disease. Several antiviral options are available for the prevention and treatment of CMV infection, each with their own specific advantages and disad-vantages. Additional antiviral agents are needed to expand the armamentarium of CMV treatment options.

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Self-Assessment Questions

Questions 1 and 2 pertain to the following case.

R.M. is a 47-year-old man with a history of cirrhosis secondary to nonalcoholic steatohepatitis. He received an orthotopic liver transplant 9 months ago. R.M. had acute kidney injury around the time of transplant, but now has normal renal function and has otherwise had an uncomplicated post-transplant course. He has completed 6 months of prophylaxis against cytomegalovirus (CMV) with valganciclovir 900 mg daily. His serostatus is organ donor CMV seropositive (D+)/organ recipient seronegative (R−). He was experiencing some fever and chills for about 3 days and decided to come to clinic today. R.M. has no other localized symptoms. His CMV PCR was checked and returns at 5110.

1. Which one of the following is best to recommend for R.M.?

    A. Do not begin antiviral therapy at this time; repeat CMV PCR in 1 week and re-assess at that time.
    B. Begin intravenous ganciclovir dosed at 5 mg/kg every 12 hours; monitor CMV PCR weekly until it becomes undetectable.
    C. Begin oral valganciclovir dosed at 900 mg twice daily; monitor CMV PCR weekly until it becomes undetectable.
    D. Begin oral valganciclovir dosed at 900 mg daily; monitor CMV PCR weekly until it becomes undetectable.

2. R.M. begins therapy with valganciclovir and you continue to monitor his CMV PCR every week. His PCR trend is the following:

    [CMV DNA IU/mL] Baseline 2110 → Week 1: 3254 → Week 2: 1249 → Week 3: 146

    He is otherwise doing well at home and his fevers have subsided. Which one of the following is best to recommend for R.M.?
    A. Continue valganciclovir therapy at 900 mg twice daily; continue monitoring CMV PCR weekly until it becomes undetectable.
    B. Switch valganciclovir therapy to intravenous ganciclovir dosed at 5 mg/kg every 12 hours because the CMV PCR is still detectable.
    C. Switch valganciclovir therapy to intravenous foscarnet dosed at 90 mg/kg every 12 hours because the CMV PCR is still detectable.
    D. Decrease the dose of valganciclovir therapy from 900 mg twice daily to 900 mg daily to transition to maintenance therapy for an additional 1 to 3 months.

Questions 3 and 4 pertain to the following case.

A.M., a 59-year-old woman with a medical history of interstitial pulmonary fibrosis, received a left single lung transplant about 1 year ago. She received 6 months of prophylaxis with valganciclovir (CMV D+/R−) and now presents with fever for 3 days, hypoxia, and dyspnea on exertion. A.M. is admitted to the medical ICU and is intubated 1 day later. Chest radiography shows new bilateral pulmonary infiltrates. A bronchoalveolar lavage (BAL) is performed and returns with a CMV PCR of 101 IU/mL.

3. Which one of the following best assesses A.M.'s presentation?

    A. Proven CMV pneumonia because she has clinical signs and symptoms as well as CMV isolated in BAL fluid.
    B. Probable CMV pneumonia because she has clinical signs and symptoms as well as CMV D+/R− status.
    C. Probable CMV pneumonia because she has clinical signs and symptoms as well as CMV isolated in BAL fluid.
    D. Proven CMV pneumonia because she has radiographic changes consistent with pneumonia, as well as CMV isolated in BAL fluid.

4. A.M.'s medical team initiates valganciclovir therapy for her CMV. Which one of the following are most pertinent to monitor for while A.M. is receiving valganciclovir therapy?

    A. CBC, blood urea nitrogen (BUN), serum creatinine
    B. Electrolytes, BUN, serum creatinine
    C. BUN, serum creatinine, ECG
    D. CYP3A drug−drug interactions, CBC

5. A 64-year-old man presents to an outpatient clinic visit after a bilateral lung transplant 1 month ago. He is overwhelmed with the amount of medications he now has to take and is questioning his valganciclovir prophylaxis. He states he has heard this medication is not always necessary after transplant. Which one of the following is the best counseling point to give this patient?

    A. Switching to pre-emptive therapy is an option but involves frequent monitoring of CMV PCR levels without having to take valganciclovir daily.
    B. Because he received a lung transplant, universal prophylaxis with valganciclovir daily is the best option to prevent CMV infection and/or disease.
    C. Valganciclovir is always to be taken daily after transplant, regardless of the type of transplant.
    D. Switching to pre-emptive therapy is an option but should only be pursued if the patient prefers to not take valganciclovir.

6. Which one of the following patients has the highest risk for developing CMV infection and/or disease?

   A. A 47-year-old woman hematopoietic stem cell transplant (HSCT) recipient (CMV serostatus is organ donor CMV seronegative D−/R+) and has graft versus host disease

   B. A 53-year-old man lung transplant recipient (CMV serostatus is D+/R+) and has bronchiolitis obliterans syndrome

   C. A 64-year-old woman acute myeloid leukemia patient who is 4 days status-post induction chemotherapy with daunorubicin and cytarabine (7+3)

   D. An 87-year-old man HSCT recipient (allogeneic cord blood transplant; CMV serostatus is D−/R−) and who has received a myeloablative conditioning regimen with fludarabine and busulfan

7. A 63-year-old man has a medical history of a deceased donor kidney transplant 1 year ago which was complicated by drug-resistant CMV. The patient was transferred from an outside hospital while on cidofovir 5 mg/kg every other week, which is the only antiviral that is susceptible per outside records. The patient's serum creatinine has increased to 0.9 mg/dL from his baseline of 0.6 mg/dL, and has 1+ proteinuria. Which one of the following is best to recommend for this patient?

   A. Discontinue cidofovir at this time due to increase in serum creatinine.

   B. Dose adjust cidofovir to 3 mg/kg every other week due to increase in serum creatinine.

   C. Continue cidofovir at 5 mg/kg every other week and administer with an additional 1 L of normal saline.

   D. Continue cidofovir at 5 mg/kg but increase frequency to every 4 weeks.

8. A 53-year-old woman underwent a deceased donor kidney transplant in 3/2018 (D+/R−). She received induction immunosuppression with basiliximab and is currently on tacrolimus, mycophenolate mofetil, and prednisone for maintenance immunosuppression. The patient has had a relatively uncomplicated course since her transplant, experiencing two urinary tract infections in the past 2 years. Which one of the following is this patient's greatest risk factor for developing CMV infection/disease?

   A. Basiliximab induction
   B. Tacrolimus immunosuppression
   C. Urinary tract infection
   D. CMV D+/R− transplant

9. Three days ago, a 59-year-old man underwent an orthotopic heart transplant (CMV D+/R+). He has normal renal function and no drug allergies. Which one of the following is best to recommend for this patient for prophylaxis against CMV?

   A. Ganciclovir 5 mg/kg intravenously every 12 hours
   B. Acyclovir 400 mg orally twice daily
   C. Foscarnet 90 mg/kg intravenous once daily
   D. Valganciclovir 900 mg orally once daily

Questions 10–12 pertain to the following case.

E.K., a 32-year-old woman with a medical history of alcoholic cirrhosis, underwent an orthotopic liver transplant about 7 months ago (CMV D+/R−). She completed her prophylaxis with valganciclovir about 1 month ago and is now found to have CMV DNAemia (23,584 IU/mL). E.K. has had associated fever (maximum temperature 102.1°F [38.9°C]), chills, nausea, and diarrhea 5–7 times per day for the past 10 days.

10. Which one of the following is best to recommend for E.K.?

    A. Ganciclovir 5 mg/kg intravenously every 12 hours
    B. Foscarnet 90 mg/kg intravenously every 12 hours
    C. Valganciclovir 900 mg orally twice daily
    D. Cidofovir 5 mg/kg intravenously once weekly

11. E.K.'s medical team asks for information regarding CMV intravenous immune globulin (CMVIg). Which one of the following is the best information to share with E.K.'s care team regarding CMVIg?

    A. It is only indicated for CMV prophylaxis in solid organ transplant (SOT) patients, but is sometimes used off-label for adjunctive CMV treatment.

    B. It is not commonly used because of dose-limiting toxicities and difficult administration procedures.

    C. It is not commonly used because of a lack of clinical data in SOT patients.

    D. It is another monotherapy option for the treatment of drug-resistant CMV.

12. E.K. has a genotype return while on foscarnet therapy and she has a confirmed UL97 mutation. She is otherwise doing well, she is afebrile, and her diarrhea symptoms have resolved. E.K.'s CMV PCR trends are as follows: Week 2: 46,103 IU/mL → Week 3: 20,804 IU/mL → Week 4: 5,825 IU/mL → Week 5: Not detected → Week 6: Not detected. Which one of the following is the best CMV therapy to recommend for E.K.?

    A. Continue therapy; switch to cidofovir for 1–3 additional months.

    B. Continue therapy; switch back to ganciclovir for 6 additional months.

    C. Discontinue therapy.

    D. Discontinue therapy; begin letermovir for prophylaxis.

13. A 42-year-old woman with a medical history of non-ischemic cardiomyopathy received an orthotopic heart transplant about 7 years ago (CMV D+/R+). She had an uneventful post-operative course. She completed 3 months of valganciclovir prophylaxis and now is admitted to the hospital with coronavirus disease 2019 (COVID-19) pneumonia after being around others without masks. The patient is receiving symptomatic treatment and is intubated in the ICU. A CMV PCR was sent and returns at 61 IU/mL. Which one of the following is best to recommend for this patient?

    A. Initiate CMV therapy with valganciclovir 900 mg orally twice daily; monitor CMV PCR in 1 week.
    B. Repeat CMV PCR in 1 week; monitor for any new signs and/or symptoms of CMV infection/disease.
    C. Initiate CMV therapy with ganciclovir 5 mg/kg intravenously every 12 hours; monitor CMV PCR in 1 week.
    D. Initiate CMV prophylaxis with valganciclovir 900 mg orally daily; monitor CMV PCR in 1 week.

14. A physician approaches you about a clinic patient with CMV DNAemia and intolerances to multiple different therapies. This colleague wants to know more information about maribavir. Which one of the following is the best educational point about maribavir to share with this colleague?

    A. It is currently FDA approved for CMV treatment in SOT recipients.
    B. It is currently FDA approved for CMV prophylaxis in R+ HSCT recipients.
    C. It is not yet FDA approved and is most commonly limited by the side effect of dysgeusia.
    D. It is not yet FDA approved and is most commonly limited by the side effect of neutropenia.

15. A 48-year-old woman with acute myeloid leukemia underwent a matched unrelated donor hematopoietic stem-cell transplant 3 days ago (D−/R+). She is immunosuppressed with tacrolimus and methotrexate. Which one of the following is best to recommend for CMV prevention for this patient?

    A. Valacyclovir 1 g three times daily for 100 days
    B. Valganciclovir 900 mg daily for 100 days
    C. Letermovir 480 mg daily for 100 days
    D. Acyclovir 400 mg twice daily for 100 days