Novel Treatment Advances and Approaches in the Prevention and Management of Cytomegalovirus (CMV) Infection

A CME/CNE Approved Activity

JOURNAL of MANAGED CARE MEDICINE

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Learning Objectives:
1. Discuss the impact and burden of CMV infection in transplant recipients.
2. Examine the efficacy and safety profiles of novel antivirals for the prevention and management of CMV in hematopoietic stem-cell transplant (HSCT) recipients.
3. Identify patients who may benefit from antiviral treatment for CMV infection.
4. Optimize clinical and economic strategies in the prevention of CMV in HSCT recipient.

Faculty Disclosure:
Dr. Roy F. Chemaly, MD, MPH, FACP, FIDSA is a consultant to Oxford Immunotec, Chimerix, Merck & Co., and Astellas and has received research grants from Oxford Immunotec, Chimerix, Novartis, and Merck & Co.
All material has been peer reviewed for bias.

Planning Committee Disclosure
Bill Williams, MD; Jacqueline Cole, RN, CPHQ, CMCN; and Jeremy Williams have no relevant financial relationships to disclose.

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Novel Treatment Advances and Approaches in the Prevention and Management of Cytomegalovirus (CMV) Infection

Post-Test Questions

1. Which of the following is an accurate statement about cytomegalovirus (CMV)?

   a. It is a member of the adenovirus family.
   b. Sixty to 90 percent of adults are thought to have latent CMV.
   c. A majority of individuals get their initial infection when immunocompromised.
   d. Once treated, CMV is eliminated from the body.

2. Which of the following is transfer of hematopoietic stem cells from one individual to another?

   a. Allogenic transplant
   b. Transgeneic transplant
   c. Autologous transplant
   d. Synologous transplant

3. With a hematopoietic stem cell transplant (HSCT), the risk for CMV infection begins before engraftment and continues for at least 45 days.

   a. True
   b. False

4. Which of the following is NOT a risk factor for CMV infection post-HSCT?

   a. CMV-positive serology of the marrow donor.
   b. Granulocyte transfusions from seropositive donors.
   c. Granulocyte stimulating factor use.
   d. Anti-T-cell agent use.

5. Preemptive therapy involves giving CMV active antivirals to only those patients who test positive for CMV on highly sensitive tests.

   a. True
   b. False

6. Which of the following is NOT an advantage of CMV prophylaxix compared to preemptive therapy?.

   a. Effectiveness against direct and indirect effects of CMV.
   b. Ease of use.
   c. Weekly viral load monitoring is not required.
   d. Significantly lower overall costs

7. Which of the following are FDA approved for use in preventing CMV infection in HSCT?

   a. Ganciclovir and foscarnet
   b. Ganciclovir and valganciclovir
   c. Letromir and foscarnet
   d. Letromir and ganciclovir

8. Which of the following is first-line therapy for preventing CMV infection post-HSCT?

   a. Acyclovir b. Foscarnet c. Ganciclovir d. Cidofovir

9. What is the major toxicity of foscarnet?

   a. Hepatotoxicity
   b. Nephrotoxicity
   c. Seizures
   d. Anemia

10. Which of the following antivirals is the only one which has been shown in clinical trials to impact overall mortality when used for CMV prevention?

    a. Letromir
    b. Valganciclovir
    c. Cidofovir
    d. Foscarnet

Activity Evaluation and Improvement Process

Please rate this activity on the following scale:
4 - Excellent 3 - Good 2 - Fair 1 - Poor

1. Based on the content presented, I am better able to:

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   4 3 2 1

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7. Did the content of the activity help in meeting your above goal?

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Novel Treatment Advances and Approaches in the Prevention and Management of Cytomegalovirus (CMV) Infection

Roy F. Chemaly, MD, MPH, FACP, FIDSA

Introduction

CYTOMEGALOVIRUS (CMV) IS A GLOBALLY ubiquitous member of the herpesvirus family that infects a majority of individuals by adulthood, typically producing mild symptoms or none at all. As with the other herpesviruses, CMV remains in the human body after the primary infection for life. Sixty to 90 percent of adults are thought to have latent CMV. Infection or reactivation of latent CMV in individuals with weakened immune systems can lead to severe complications, including end-stage organ disease and invasive CMV disease. Patients undergoing solid organ transplant or hematopoietic stem cell transplant (HSCT) are particularly vulnerable to CMV infections due to immunosuppression. The focus of this monograph is CMV infections after HSCT.

HSCT Background

HSCT is the transfer of hematopoietic cells from one individual to another (allogeneic HSCT) or the return of previously harvested cells to the same individual (autologous HSCT) after manipulation of the cells and/or the recipient.[1] Recipients of a HSCT will usually undergo a conditioning regimen of chemotherapy with or without total body irradiation before the transplant. Engraftment is the term for when the transplanted cells have moved to the bone marrow of the recipient and begin to reproduce. All HSCT recipients experience a prolonged period of immunosuppression characterized by profound defects in cell-mediated and humoral immunity.

Allogeneic HSCT can cure or improve outcome in leukemia, lymphoma, myeloproliferative disorders, myelodysplasia, bone marrow failure syndromes, congenital immunodeficiencies, enzyme deficiencies, and hemoglobinopathies. Significant morbidity and mortality due to conditioning-related toxicity, opportunistic infection, and graft-versus-host disease (GVHD) can occur with allogeneic HSCT. Autologous HSCT can improve outcomes in acute and chronic leukemia, multiple myeloma, severe autoimmune disease, amyloidosis, and Hodgkin's disease and non-Hodgkin's lymphoma. Conditioning-related toxicity and infections contribute to the morbidity and mortality associated with autologous HSCT; however, morbidity due to GVHD generally does not occur after this procedure.[1]

Burden of CMV with HSCT

Patients who have undergone a HSCT are at risk for various bacterial, fungal, and viral infections for at least one year after the procedure, until their immune system has completely recovered. Exhibit 1 shows that the risk for CMV infection begins before engraftment and continues out to at least one year.[1] CMV infection remains among the most common and significant complication after HSCT. It may have a deleterious impact on the overall outcome after transplantation. Approximately 30 percent of seronegative recipients (R-) transplanted from a seropositive donor (D+) develop primary CMV infection.[2] Without prophylaxis, approximately 80 percent of CMV-seropositive patients (R+) experience CMV infection after allogeneic HSCT.[3] After autologous HSCT, approximately 40 percent of seropositive patients develop CMV infection.[2] Patients who have GVHD are at increased risk for CMV infection which is proportional to the severity of the GVHD.[4]

Direct effects of CMV include pneumonia, gastrointestinal disease, hepatitis, and retinitis. The incidence of CMV pneumonia ranges from 1 percent to 6 percent in autologous HSCT recipients and 10 percent to 30 percent in allogeneic HSCT recipients.[5] In addition to the direct effects of CMV infection, indirect effects, which may be due to the immunosuppressive nature of the virus, may be associated with increased risk of GVHD, graft rejection, myelosuppression, and invasive bacterial and fungal infections.[6]

Treating CMV infections in HSCT patients is costly. The overall total costs of a CMV encounter has been estimated at over $42,000 in direct costs per patient.[7] CMV resulted in a mean length of

Exhibit 1: Timing of CMV Risk After HSCT[1]			
	Phase 1: Pre-engraftment	Phase II: Post-engraftment	Phase II: Late Phase
Immune Defects	Neutropenia, barrier breakdown (mucositis, central venous access devices)	Impaired cellular and humoral immunity; NK cells recover first, CD8 T cell numbers increasing but restricted T cell repertoire	Impaired cellular and humoral immunity, B cell and CD4 T cell numbers recover slowly and repertoire diversifies

hospital stay of 14.92 days, an intensive care unit stay in 20 percent of patients, an intensive care unit median stay of 10.35 days, and death in 10.7 percent of cases.[7] If adverse effects from the antiviral therapy occur, costs also increase. Nephrotoxicity with foscarnet doubled the cost of care.

Diagnosis

The presence of CMV antibodies (IgM and IgG antibody to CMV) can indicate a new CMV infection, but much CMV disease in transplant patients results from reactivation of latent disease in the immunocompromised host. Reactivation of CMV can result in virus in the urine and in other body fluids or tissues; however, the presence of CMV in body fluids and tissues does not always indicate disease and may merely represent shedding.[8] CMV-induced abnormalities on biopsy may be necessary to demonstrate invasive disease. Quantitative detection of CMV antigen or DNA in the peripheral blood can also be very helpful because elevated or rising CMV titers are often highly suggestive of invasive disease.[8]

Prevention of CMV Post Transplant

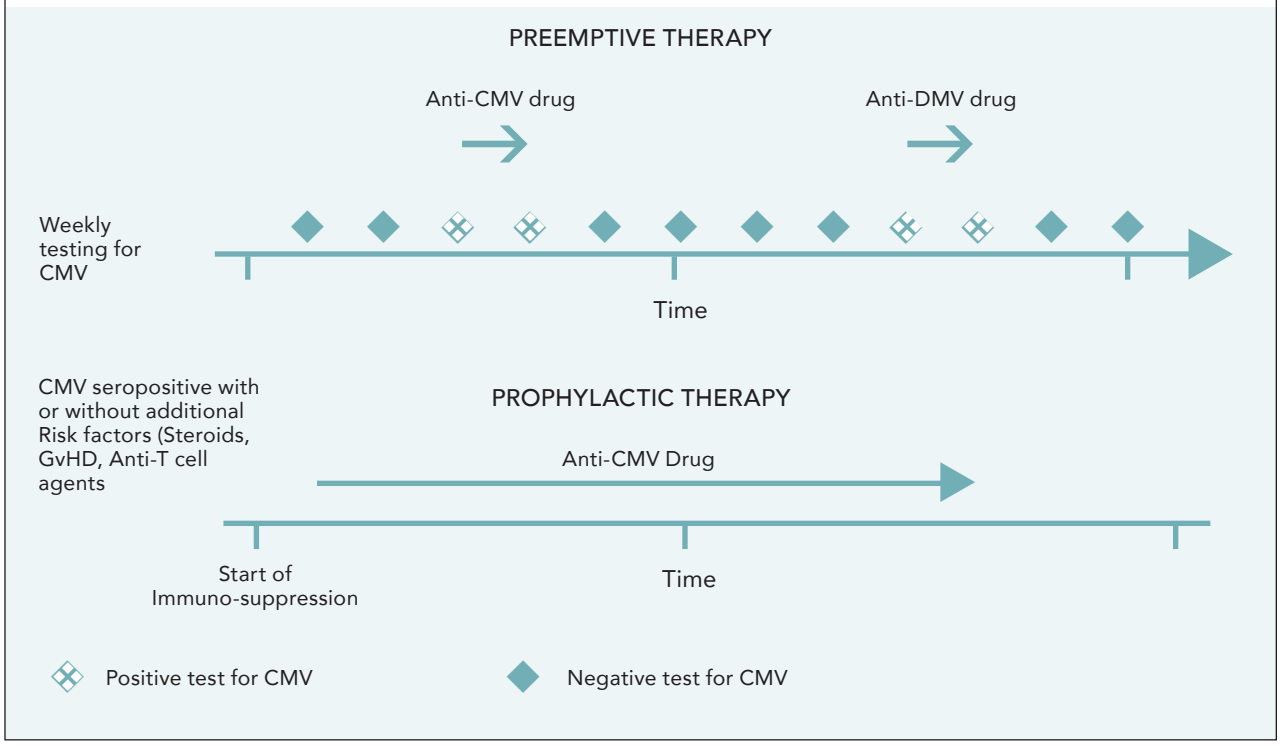
Current CMV prevention strategies after HSCT include prophylactic and preemptive therapy (Exhibit 2). Prophylaxis is giving everyone with risk factors for CMV infection antiviral medication active against CMV from the start of immunosuppression through the time period with the highest risk for reactivation of CMV. Risk factors include positive serology of the marrow donor, granulocyte transfusions from seropositive donors, acute GVHD, corticosteroid use, and anti-T-cell agent use. Prophylaxis was most common until about 1995 when the use of preemptive therapy began to increase; it is now most commonly used. Preemptive therapy involves giving CMV active antivirals to only those patients who test positive for CMV on highly sensitive tests [pp65 antigenemia (pp65 Ag), CMV DNA amplification in peripheral blood leukocytes (PBL) and plasma, and CMV late mRNA amplification] before they develop disease. Patients are tested weekly and treated if viral loads surpass a particular threshold. Therapy is continued until viral loads decline, and it is then stopped.

The advantages of prophylaxis include effectiveness against direct and indirect effects of CMV and its ease of use. Weekly viral load monitoring is not required. Disadvantages include overtreatment, which exposes individuals who may not develop CMV to medication toxicity, possible delay in immuno-reconstitution post-transplant (this is controversial), and cost.

The advantages of preemptive therapy are that it targets therapy to patients at highest risk, which minimizes overtreatment and toxicity and it may improve CMV-specific immune reconstitution. Preemptive therapy can miss cases of CMV disease that are not preceded by viremia, especially gastrointestinal disease. Other disadvantages are reliability on availability of sensitive CMV testing and costs.

Costs of treatment for both approaches can be high because most of the antivirals used require hospital-based intravenous therapy. One study reported a cost differential within six months after allogenic HSCT of $58,000 to $74,000 with CMV preemptive therapy, compared with no preemptive therapy.[9] Another trial found $42,000 to $56,000 as costs of preemptive therapy, depending on whether

Exhibit 2: Current CMV Prevention Strategies



ganciclovir or foscarnet, respectively, were used.[10]

Preemptive therapy has been shown to decrease the risk of CMV infection.[11] This same study found that CMV viremia was associated with an increased risk of overall mortality in the first year after HSCT, independent of the use of preemptive therapy, and with evidence of a positive dose-response relationship. Data from the Center for International Blood and Marrow Transplant Research database validated this mortality finding.[12] This database study found that the median time to CMV reactivation was 41 days after transplant, with 98 percent of reactivations occurring within the first 100 days of HSCT. Although it has been hypothesized that CMV infection can protect against hematologic disease relapse post-transplant, this study found there was no protective effect of CMV infection. CMV reactivation and positive CMV serostatus were associated with high non-relapse mortality, regardless of what hematologic disease (acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, and myelodysplastic syndrome) led to the transplant.

Viral loads can also be used to determine need for preemptive therapy; however, clinicians have a difficult decision to make about treatment when a patient has a low level of CMV detected. The combination of viral load monitoring with monitoring of CMV-specific T-cell immunity is being investigated to optimize prevention in HSCT recipients. This strategy may allow withholding preemptive therapy or prophylaxis in patients with low-to-moderate levels of CMV DNA, in the presence of CMV-specific T-cell responses. Several observational studies now show a link between T-cell immunity and CMV viremia. One example T-cell response assay is ELISPOT (T-SPOT® CMV). In one study of the ELISPOT CMV assay for pp65 and IE1 antigens, patients with higher T-cell response tended to not progress to high CMV levels.[13] Studies in which a T-cell response assay is used in real time to make clinical decisions are ongoing. These clinical decisions include stopping prophylaxis early, initiating antiviral treatment for low-level viremia, and withholding secondary prophylaxis from patients who finish CMV therapy and have a positive CMV cell-mediated immunity response (CMI). More interventional clinical studies are necessary before CMI assays become routine clinical practice.

Overall, HSCT recipients at risk for post-transplant CMV disease (i.e., all CMV-seropositive HSCT recipients and all CMV-seronegative recipients with a CMV-seropositive donor) should be placed on a CMV disease prevention program from the time of engraftment until at least 100 days after HSCT.[1] If a prophylactic approach is being used, antiviral therapy

is started at the time of engraftment and continued until 100 days post-transplant. If a preemptive approach is being used, the patient is tested weekly. If testing indicates CMV disease, preemptive therapy should be given for a minimum of two weeks. After two weeks of therapy, maintenance therapy is continued if virus is still detected and can be given until CMV is undetectable, or it can be continued to day 100.[1] After discontinuation of preemptive therapy, routine weekly screening is still necessary until at least day 100 because recurrent episodes of CMV viremia commonly occur. The average is two episodes per patient after transplant and can be up to five episodes.

Antivirals

Drugs for prophylaxis and preemptive therapy include ganciclovir (Cytovene®), valganciclovir (Valcyte®), foscarnet (Foscavir®), cidofovir (Vistide®), and one recently approved agent, letermovir (Prevymis®). It is important to note that only ganciclovir and letermovir are FDA approved for use in preventing CMV infection in HSCT; the other agents have been studied for this indication, but are used off-label. Ganciclovir has been the first-line drug for prophylaxis and preemptive therapy. Valganciclovir is an oral prodrug of ganciclovir and trials have shown it has similar efficacy to ganciclovir for preemptive therapy. Although foscarnet is as effective as ganciclovir, it is currently more commonly used as a second-line drug, due to practical reasons (e.g. requirement for prehydration and electrolyte monitoring) and risk for renal toxicity.

Granulocytopenia, anemia, thrombocytopenia, and pancytopenia have been reported with ganciclovir. Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, and bone marrow failure including aplastic anemia have been reported in patients treated with valganciclovir. Both agents have a black box warning about hematologic adverse effects. Dose adjustment for renal insufficiency is necessary with ganciclovir and valganciclovir in order to avoid hematologic toxicity.

Renal impairment is the major toxicity of foscarnet. Frequent monitoring of serum creatinine with dose adjustment for changes in renal function, and adequate hydration with administration of foscarnet is imperative. The adverse effects of foscarnet, which is only given intravenously, are significant and include nephrotoxicity, symptomatic hypocalcemia, hypomagnesemia, hyperphosphatemia, hypokalemia, and CNS effects.

Cidofovir is a "broad-spectrum" antiviral with a long half-life, allowing a once-per-week dosing schedule. The major toxicity with cidofovir, acute renal tubular necrosis, limits its use after a HSCT to a third-line setting. The significant adverse effects of ganciclovir/valganciclovir, foscarnet, and cidofovir, especially with long-term use, have been a challenge for clinicians to overcome.

CMV antiviral resistance is rare in HSCT patients; however, it does occur. Increasing antigenemia or CMV DNA load early after initiation of antiviral therapy is usually not a sign of treatment failure in patients who have not been previously treated with antiviral agents and therefore does not necessitate change of therapy.[1] Signs of CMV disease or levels of antigenemia or CMV DNA load that continue to rise after more than two weeks of therapy suggest resistant CMV and a change of therapy should be considered. Risk factors for drug resistance include prolonged (months) antiviral therapy, intermittent low-level viral replication caused by profound immunosuppression or suboptimal drug levels, and lack of prior immunity to CMV.[14] Patients who develop antiviral resistance are left with limited alternatives. In the absence of an approved CMV vaccine, there is a pressing need for new treatment strategies for CMV infections employing less-toxic antiviral mechanisms.

Novel Agents for CMV

Letermovir is a recently approved antiviral compound with a novel mechanism of action, which appears to be less toxic than prior therapies. It targets highly selective CMV DNA terminase, required for viral DNA processing and packaging, and is a potent inhibitor of CMV. Additionally, it is fully active against mutant CMV strains resistant to DNA polymerase inhibitors (cidofovir and ganciclovir) and wild-type CMV. Exhibit 3 compares the antiviral activity of letermovir to other approved agents and some investigational antivirals.

In a study evaluating the incidence and time to onset of prophylaxis failure in CMV-seropositive recipients of allogeneic HSCT from matched related or unrelated donors, higher doses of letermovir were more effective in preventing CMV infection (240 mg/day vs. 120 mg/day and 60 mg/day).[15] In the Phase III trial of this agent used for FDA approval, an even higher dose was safely and effectively used (480 mg/day). This dose of letermovir significantly reduced CMV infection rates at week 24 post-transplant (7.7% vs 39.4%).[16] In patients who had detectable CMV DNA at randomization, this agent prevented progression to clinically apparent infection (51.8% vs 86.6%). Importantly, letermovir treatment reduced all-cause mortality at week 24 (10.2% vs 15.9%).[16] This benefit has not been seen in any other prophylaxis or preemptive therapy trials.[17]

Exhibit 3: Antiviral Activity Comparison							
Viral Family	dsDNA Virus	Brincidofovir*	Cidofovir	Ganciclovir**	Foscarnet	Maribavir*	Letermovir
Herpes	Cytomegalovirus (CMV, HHV-5)	0.001	0.4	3.8	50 - 800	0.31	0.005
	Epstein-Barr Virus (EBV, HHV-4)	0.03	65.6	0.9	<500	0.63	>10
	Human Herpesvirus 6 (HHV-6A)	0.003	2.7	5.8	16	Inactive	>10
	Human Herpesvirus 8 (HHV-8)	0.02	2.6	8.9	177	Inactive	-
	Herpes Simplex Virus 1 (HSV-1)	0.01	3.0	0.7	92 - 95	Inactive	>10
	Herpes Simplex Virus 2 (HSV-2)	0.02	6.5	2.5	91 - 96	Inactive	>10
	Varicella Zoster Virus (VZV, HHV-3)	0.0004	0.5	1.3	39.8	Inactive	>10
Adenovirus	Adenovirus (AdV-B7)	0.02	1.3	4.5-33	Inactive	-	>10
Polyoma	BK Virus (BKV)	0.13	115	>200	Inactive	-	-
	JC Virus (JCV)	0.045	>0.1	-	Inactive	-	-
Papilloma	Human Papillomavirus 11 (HPV-11)	17	716	Inactive	-	-	-
Pox	Variola	0.1	27	-	-	-	-
	Vaccinia	0.8	46	>392	Inactive	-	-

Potency expressed as EC50 = concentration in μM required to reduce viral replication by 50% in vitro; "-" indicates no data.
* Investigational
** Valganciclovir is rapidly converted to ganciclovir in vivo. Therefore, ganciclovir is the relevant compound for cell activity studies.

Letermovir is FDA approved for prophylaxis of CMV infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic HSCT. The recommended dose is 480 mg oral or intravenous once daily initiated between days 0 through day 28 post-transplant and continued through day 100; the dose should be reduced to 240 mg daily if coadministered with cyclosporine. Letermovir is metabolized primarily by hepatic OATP1B1/3 and is not recommended for patients with severe hepatic impairment.

Letermovir appears to be a relatively well-tolerated agent with low risk of myelotoxicity and nephrotoxicity. No evidence of bone marrow suppression has been seen, even in the greater than 60 percent of study subjects who had not engrafted at baseline. Adverse effects occurring in trials at rates higher than placebo (but not necessarily statistically different) included atrial fibrillation, tachycardia, nausea, vomiting, and peripheral edema. It also does not appear to negatively impact engraftment; the incidence of engraftment was similar between letermovir (95%) and placebo (91%).[18] Median time to engraftment was similar between letermovir (19 days) and placebo (18 days).[18] In prophylaxis trials, two breakthrough infections were reported due to selection of CMV UL56 V236M mutation, so resistance may occur.[19]

Some transplant centers are now using this agent for prophylaxis in those who are CMV positive at the time of transplant. With the introduction of letermovir, prevention of CMV infection in allogeneic HSCT recipients will likely shift considerably, from a predominantly preemptive strategy to one that utilizes this novel therapy for prophylaxis.

Investigational Agents for CMV

There are several agents under study for preventing and treating CMV infection. Brincidofovir, an investigational prodrug of cidofovir, is a broad-spectrum antiviral agent. Proprietary lipid technology allows oral, twice-weekly dosing which delivers active antiviral to the intracellular space. In one trial, this agent was given twice a week for 14 weeks after transplant. Twenty-four percent of those on the study-drug developed CMV reactivation, compared with 38 percent of the placebo group during the treatment phase, and 22 percent developed it during the follow-up period, compared with 11 percent in the placebo group.[20] By 168 days after the transplant, the rates of CMV were almost equal in the two groups. This negative finding may have been due to GVHD diagnoses and treatment. The median cumulative exposure to corticosteroids was eightfold higher in subjects in the treatment arm

of this study than those on placebo.

Maribavir is another novel anti-CMV drug that acts by disrupting viral DNA packaging and viral egress rather than DNA replication. It is a potent member of a new class of drugs, the benzimidazole ribosides. It inhibits the CMV UL97 kinase by competitively inhibiting the binding of ATP to the kinase ATP-binding site. It is active against wild-type and ganciclovir-resistant CMV strains. Compared to ganciclovir, foscarnet, and cidofovir, maribavir is a highly potent anti-CMV agent.[21]

Clinical progression of maribavir stalled after a Phase III trial failed to prevent CMV infections in HCST patients, but later analysis identified flaws in the study's selected dosage (100mg taken orally twice-daily) and primary endpoint (CMV disease).[22] A subsequent trial using higher dosages (400 – 1,200mg taken orally twice-daily) found that maribavir effectively eliminated plasma CMV DNA in solid organ transplant and HSCT patients who were resistant or refractory to standard therapy. Notably, no myelosuppression or other major toxicities were observed with maribavir therapy.[23]

An ongoing Phase III, multicenter, randomized trial is now evaluating the safety and efficacy of maribavir (400mg taken orally twice-daily) in transplant recipients. Focusing on subsets of vulnerable individuals, the trial is comparing maribavir to investigator-assigned anti-CMV therapy in patients who are resistant or refractory to at least one existing treatment, with a primary endpoint of CMV viremia clearance.

Conclusion

CMV serostatus and reactivation remains an important variable affecting transplant outcomes, including GVHD incidence, graft failure/rejection, non-relapse mortality, and overall survival. Letermovir is a new, novel antiviral agent with a different mechanism of action with the potential to render prophylactic therapy more feasible and less toxic. Additional new antiviral drugs, immune monitoring, and prophylactic strategies will likely have a major impact on patient outcomes in coming years.

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Notes