Antiviral therapy for cytomegalovirus infections in pediatric patients

David W. Kimberlin MD, PhD
Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL 1045-1870/02/1301-0006$35.00/0 Available online 10 January 2005.

Abstract

Appreciation of the spectrum of illness caused by cytomegalovirus (CMV) infections has increased markedly during the past 2 decades. The number of immunosuppressed patients with CMV has increased during the same time period, reflecting the central tenet that CMV disease is rare in this patient population. Fortunately, antiviral therapies with activity against CMV have been identified during this same time course, and they include ganciclovir, foscartern, and cidofovir. Although all 3 of these therapies can have significant toxicities associated with them, nonetheless, they are employed with relative frequency to treat potentially life-threatening CMV disease. Ganciclovir is the first-line compound used, followed by foscartern and cidofovir. This article summarizes those CMV infections that require antiviral therapy and outlines the specific clinical criteria for each. Copyright 2002, Elsevier Science (USA). All rights reserved.

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Although successful antiviral therapies against herpesvirus infections were available as early as the mid-1970s, it was with the commercial introduction of acyclovir in 1982 that therapeutic interventions for herpesvirus diseases in the pediatric population began to come of age. The extraordinary specificity of action and the safety profile of acyclovir render it a truly unique antiviral agent. Despite these beneficial qualities of acyclovir, soon after its development, acyclovir was recognized as having very limited activity against cytomegalovirus (CMV) infections. Only with the subsequent development of ganciclovir, foscarin, and cidofovir have truly effective means of treating CMV infection become available. However, each of these compounds has significant toxicities that frequently limit its use. This article provides an overview of CMV and of each of the antiviral agents used in the treatment of pediatric CMV infections and disease.

CMV

Human CMV is a member of the β-herpesviruses, along with human herpesvirus-6 and human herpesvirus-7. As with all human herpesviruses, CMV DNA is contained within a nucleocapsid of 162 hexagonal capsomeres. The nucleocapsid is surrounded by an ill-defined tegument, which in turn is surrounded by a loosely applied lipid envelope. Based on restriction enzyme analysis of viral DNA, multiple genetic variants, or strains, of CMV exist. Persons infected with 1 strain of CMV show cross-reactive immunity against all strains, although the extent to which it provides cross-protection from CMV disease remains to be defined.

CMV encodes for approximately 175 unique proteins, 2 of which are of particular interest as they relate to antiviral therapy: (1) the CMV DNA polymerase, encoded by UL54, is homologous to the DNA polymerase encoded by other members of the Herpesviridae family and (2) the CMV phosphotransferase encoded by UL97 is the functional equivalent of the thymidine kinase of herpes simplex virus (HSV) and varicella zoster virus (VZV), and as such is responsible for phosphorylating antiviral drugs. The role of UL97 in the normal replicative cycle of CMV has not been elucidated. Interestingly, the UL97 homolog in HSV does not phosphorylate nucleoside drugs and functions exclusively as a protein kinase.[1]

CMV is a ubiquitous virus, and humans are its only reservoir. In general, the prevalence of CMV infection is
higher in developing countries and among the lower socioeconomic strata of developed nations. These
differences are particularly striking during childhood. The modes of transmission from person to person are not
completely understood.[2] In most individuals, including congenitally and perinatally infected babies, CMV
infections are subclinical. Virus excretion persists for years after congenital, perinatal, and early postnatal
infections. Prolonged viral shedding also is a feature of primary infection in older children and adults. Each of
these infected persons continues to expose other susceptible people. Because recurrent infections are fairly
common occurrences, intermittent excretion of virus can be anticipated in a significant proportion of seropositive
adults. Each of these circumstances provides a large reservoir of CMV in the population at any given time.

Transmission of CMV occurs by direct or indirect person-to-person contact. Sources of virus include urine,
oralpharyngeal secretions, cervical and vaginal secretions, semen, milk, tears, blood, and transplanted organs.[3
and 4] The spread of infection requires close or intimate contact with infected secretions, including sexual
contact. [3, 5 and 6] Other modes of transmission include intruterine transmission. [7] perinatal acquisition from
breastfeeding. [4] and spread among children in group child care facilities. [6 and 9] For the last group,
transmission is the result of horizontal transmission from child to child through saliva on hands and toys. [10, 11
and 12] This mode of viral transmission is so efficient that excretion rates as high as 20 to 40 percent in young
toddlers attending daycare are not unusual. Young children acquiring primary CMV infections at daycare facilities
are at risk of transmitting to them to their seronegative parents, which in turn can lead to intruterine
transmission should a mother be pregnant at the time. [13, 14 and 15] Seronegative caretakers working in
daycare centers also are at increased risk of acquisition of CMV infection. [16]

Intruterine infection presumably occurs after instances of maternal viremia and associated placental infection.
Intruterine transmission of CMV occurs in approximately 40 percent of pregnant women with primary infection.
[7] Women who do not transmit CMV transplacentally may have better cell-mediated and neutralizing antibodies
than do those who transmit the infection to the developing fetus. [17] Approximately 1 percent of seropositive
women transmit CMV in utero, but at present no laboratory markers identify those most at risk. Nearly 10 percent
of congenitally infected babies have clinically apparent neonatal disease; of these, as many as 90 percent of
survivors develop significant neurologic sequelae. [7, 18, 19 and 20] including hearing deficits in 30 to 65 percent
of patients. [19 and 21]

CMV also can be transmitted by blood transfusion, albeit infrequently. Transmission occurs in only 1 to 5 percent
of seronegative recipients exposed to seropositive blood. Exclusion of seropositive units can eliminate the risk of
transmission. With organ transplantation, on the other hand, the risk of transmission can be quite high. Whereas
seronegative patients receiving solid organ transplantation are at no risk of incurring primary infection from
seronegative donors, a seropositive organ transmits the virus in 60 to 80 percent of cases. In contrast, CMV
disease among bone marrow transplant recipients is derived from the recipient rather than the donor. [22]

In populations with higher socioeconomic conditions, approximately 40 percent of adolescents are seropositive,
with another 1 percent seroconverting annually thereafter. [23] Approximately 70 percent of adults from higher
socioeconomic strata and 90 percent from lower socioeconomic strata eventually become infected with CMV.

After primary infection, CMV persists either in a true latent form or in a state of low-level replication. Thus,
individual cells could exhibit CMV latency, whereas particular organs could always have some cells producing
virus particles. Occasional reactivations of CMV are almost always asymptomatic but allow for the spread of
CMV to other persons, either horizontally or vertically. Reinfection with another, or possibly the same, strain of
CMV also can occur. The term recurrent infection often is used when infection is nonprimary, but usually it is not
possible to differentiate reactivation from reinfection.
Antiviral agents available to treat CMV infections

Ganciclovir

Ganciclovir is a nucleoside analogue that, compared with acyclovir, has an extra hydroxymethyl group on the acyclic side chain.[24] Its greatest in vitro activity is against CMV, although it is active also against HSV-1, HSV-2, and VZV. As with many other nucleoside analogues used to treat herpesvirus infections, the first step in ganciclovir phosphorylation in infected cells is performed by a virus-encoded enzyme, converting ganciclovir to its monophosphate derivative. Di-phosphorylation and tri-phosphorylation are accomplished subsequently by cellular enzymes, yielding ganciclovir's active triphosphate moiety. In CMV-infected cells, this virus-specific enzyme is encoded by the UL97 gene.[25 and 26] Intracellular ganciclovir triphosphate concentrations are at least ten-fold higher in CMV-infected cells than in uninfected cells. [27] and intracellular ganciclovir triphosphate has a half-life of greater than 24 hours. Ganciclovir triphosphate serves as a competitive inhibitor of herpesviral DNA polymerases, although it also has some activity against cellular DNA polymerases. This potential for incorporation into cellular DNA accounts for ganciclovir's significant toxicity. Incorporation of ganciclovir triphosphate into the growing viral DNA chain results in the slowing and subsequent cessation of DNA chain elongation. [28]

Peak serum concentrations of ganciclovir attained after 5 mg/kg is administered intravenously range from 8 to 11 μg/mL.[24] At this dose, ganciclovir concentrations in aqueous humor, subretinal fluid, cerebrospinal fluid, and brain tissue are adequate for the inhibition of sensitive CMV isolates. Most of an administered dose of ganciclovir is eliminated unchanged in the urine, with an elimination half-life of 2 to 3 hours. [29] Reduction of dose roughly proportional to the degree of reduction in creatinine clearance is necessary in persons with impaired renal function. [30 and 31] Because ganciclovir is removed efficiently by hemodialysis, a supplemental dose is recommended after the patient undergoes dialysis. [30]

The pharmacokinetics of ganciclovir in the neonatal population are similar to those of adults.[32] After intravenous administration of 6 mg/kg of ganciclovir, peak concentrations of 7.0 μg/mL are achieved. The mean elimination half-life is 2.4 hours.

Intravitreal drug concentrations achieved during intravenous induction therapy average 1 μg/mL, and subretinal concentrations are comparable with those achieved in plasma.[33 and 34] Concentrations of ganciclovir in the central nervous system range from 24 to 70 percent of those in the plasma, with brain concentrations of approximately 38 percent of plasma levels. [35]

Oral bioavailability of ganciclovir is poor, with less than 10 percent of the drug being absorbed after oral administration.[36] However, the monovalyl ester prodrug of ganciclovir, valganciclovir, recently was approved by the Food and Drug Administration for the treatment of CMV retinitis. Valganciclovir is converted rapidly to ganciclovir on absorption. [37] Once converted to ganciclovir, the mechanism of antiviral activity is presumed to be the same as that described for ganciclovir. Valganciclovir is available only commercially in tablet formulation, although a syrup formulation is being investigated by the National Institute of Allergy and Infectious Disease Collaborative Antiviral Study Group for the treatment of infants with symptomatic congenital CMV disease involving the central nervous system.

Ganciclovir resistance among CMV isolates is conferred by mutations in either the UL97 gene or the CMV DNA polymerase encoded by the UL54 gene. Of these 2 mechanisms, ganciclovir-resistant CMV isolates with mutations in the UL97 open-reading frame are the predominant phenotype.[38]
**Foscarnet**

Foscarnet is an inorganic pyrophosphate analogue that inhibits all known human herpesviruses, including most ganciclovir-resistant CMV isolates and acyclovir-resistant HSV and VZV strains. It also is active against the human immunodeficiency virus (HIV). This antiviral agent directly inhibits DNA polymerase by blocking the pyrophosphate binding site and preventing cleavage of pyrophosphate from deoxynucleotide triphosphates. It is a noncompetitive inhibitor of viral DNA polymerases or HIV reverse transcriptase, and it is not incorporated into the growing viral DNA chain. It is approximately 100-fold more active against viral enzymes than host cellular enzymes.

Foscarnet is administered only by intravenous route. Data are limited regarding tissue distribution, but cerebral spinal fluid concentrations are approximately two-thirds of those in serum. Eighty percent of an administered dose of foscarnet is eliminated unchanged in the urine; half-life is 48 hours, and dosage adjustments are necessary even in the presence of minimal degrees of renal dysfunction. Hemodialysis efficiently eliminates foscarnet and, therefore, an extra dose of drug is recommended after a dialysis run. No pharmacokinetic data exist for foscarnet in neonates.

Resistance to foscarnet occurs as a result of DNA polymerase mutations. Strains of CMV, HSV, and VZV with 3- to 5-fold reduced sensitivity to foscarnet have been reported. These isolates may respond to therapy with acyclovir or cidofovir.

**Cidofovir**

Cidofovir is a new acyclic phosphonate nucleoside analog with a mechanism of action that is similar to those of other nucleoside analogues. Unlike acyclovir and ganciclovir, cidofovir already has a single phosphate group attached to its native state. As such, viral enzymes are not required for initial phosphorylation of the drug. Rather, cellular kinases sequentially attach 2 additional phosphate groups, converting cidofovir to its active diphosphate form. This active compound then serves as a competitive inhibitor of DNA polymerase. Although cidofovir is taken up by both virally infected and uninfected cells, the active form of the drug exhibits a 25- to 50-fold greater affinity for the viral DNA polymerase as compared with the cellular DNA polymerase, thereby selectively inhibiting viral replication.

Cidofovir has activity against HSV and CMV. Because of its unique phosphorylation requirements for activation, the drug usually maintains activity against acyclovir-resistant and foscarnet-resistant HSV isolates, as well as ganciclovir-resistant and foscarnet-resistant CMV mutants. Cidofovir exhibits marked activity against CMV, with inhibitory concentrations of 0.1 μg/mL for susceptible clinical isolates.

After intravenous administration of cidofovir, plasma half-life is 2.6 hours, though cidofovir persists in cells for prolonged periods. In addition, active intracellular metabolites of cidofovir have long half-lives of 17 to 48 hours. Such prolonged intracellular activity allows for an intermittent dosing schedule that is attractive when compared with ganciclovir or with foscarnet. Ninety percent of the drug is excreted in the urine, primarily by renal tubular secretion.

**Indications for antiviral therapy in healthy children**

**Disease syndromes, diagnosis, and indications for treatment**
Primary CMV infection in the immunocompetent child or adult almost always is asymptomatic, except for occasional cases of infectious mononucleosis. These latter patients present with a fever spiking over 38°C and with few localizing symptoms. Pharyngitis, lymphadenopathy, and splenomegaly are less common occurrences than in Epstein-Barr virus mononucleosis. Laboratory tests show biochemical hepatitis, with moderately raised transaminases, lymphocytosis with atypical mononuclear cells, and a negative result for heterophile agglutinins. The condition resolves spontaneously, with a mean of 19 days' fever noted in 1 large study.[51] Diagnosis of immunocompetent individuals with CMV mononucleosis typically is accomplished by serology. A positive CMV IgM suggests recent infection. Given the fact that most immunocompetent persons infected with CMV are asymptomatic and that those with symptomatology resolve their infections spontaneously, antiviral therapy of CMV infection in the healthy child is not indicated.

Indications for antiviral therapy in high-risk populations

Disease syndromes, diagnosis, and indications for treatment

In the immunocompromised host, active CMV infections cause a wide spectrum of disease, ranging from asymptomatic to life-threatening. The unifying feature of CMV disease in the immunocompromised transplant recipient is the presence of fever. It typically follows a spiking pattern, with temperatures in the range of 38°C to 40°C, followed by precipitous declines below 37°C. During the fever, the patient complains of malaise and lethargy and may develop myalgia or arthralgia. This systemic phase of CMV may resolve spontaneously or may herald particular clinical syndromes that vary in incidence according to the underlying cause of the immunocompromised state. CMV disease presents in the first and second months after receiving a transplant or, in patients with acquired immunodeficiency syndrome (AIDS) whose CD4 count has declined to less than 50 cells/μL, when the patient is most profoundly immunocompromised.

Solid organ allograft recipients

During CMV infections in this population, leukopenia occurs commonly and may be profound. Biochemical evidence of hepatitis often is found, with transaminase levels raised 2 to 3 times the upper healthy limit. Thrombocytopenia, with serial daily platelet counts less than 100,000, may occur. Pneumonitis with interstitial infiltrates may occur, especially in recipients of lung (or heart-lung) transplants. Likewise, CMV has been implicated in the development of accelerated atherosclerosis after cardiac transplant[52] or graft rejection and graft atherosclerosis.[53 and 54] These conditions present as dysfunction of the transplanted organ, with no clinical symptoms or signs that show the underlying contribution from CMV.

Diagnosis may be achieved by histopathologic evaluation of biopsies from affected organs, which show the characteristic intranuclearowl's eye inclusions with a surrounding halo and margined chromatin. Serial monitoring for viremia (blood buffy coat culture or blood/plasma PCR) and pp65 antigenemia also is employed in the assessment of acquisition or reactivation of CMV infection in the solid organ transplant recipient. These diagnostic modalities allow for use of antiviral agents to treat CMV infection/disease in 4 ways: (1) prophylactic administration to prevent development of infection, (2) suppressive therapy to prevent reactivation of latent CMV, (3) preemptive therapy to treat CMV infection before it progresses to CMV disease, and (4) treatment of documented, established CMV disease. The use of individual antiviral drugs to achieve each of these goals is discussed by antiviral agent below.

Bone marrow transplant recipients

Pneumonitis is the major life-threatening presentation of CMV in this population, occurring in 10 to 20 percent of
bone marrow allograft patients. Patients present with fever, hypoxia, and associated interstitial infiltrates of the lung. This complication is much less common (less than 5%) after autografting. CMV may delay marrow engraftment by replicating in bone marrow stromal supporting cells.[55] An important clinical feature is that CMV disease, especially pneumonitis, is statistically associated with graft-versus-host disease.[56] Whether CMV infection can precipitate graft-versus-host disease or whether the immunosuppressive nature of graft-versus-host disease or the treatment required for its suppression facilitates CMV reactivation is not clear. Diagnosis of CMV infection and disease in the bone marrow transplant recipient is the same as that for the solid organ transplant population noted previously.

**Patients with AIDS**

Before the highly active antiretroviral treatment era, at least 25 percent of patients with AIDS developed disease attributable to CMV. The vast majority (85%) of these cases were retinitis, a clinical manifestation that rarely occurs in transplant recipients. Patients with retinitis may complain of floaters or loss of visual acuity. Alternatively, a typical focus of retinitis may be recognized at routine follow-up visits. Early lesions may be white because of edema, necrosis, or both. Without treatment, the focus of infection spreads to involve neighboring cells, leaving white necrosis at the advancing border.[57] Hemorrhage surrounding blood vessels, with or without perivascular sheathing, occurs. It may be accompanied by anterior uveitis, retinal edema, or retinal detachment. Diagnosis of CMV retinitis relies largely on the clinical appearance of the retinal lesions on ophthalmologic examination.

CMV also may involve the gastrointestinal tract to cause ulcers deep in the submucosal layers. Clinical features vary with the anatomic site involved. Odynophagia is a common presentation of CMV esophagitis, whereas abdominal pain and hematochezia frequently occur with CMV colitis. Ulceration at these sites may cause perforation or hemorrhage. Histopathologic evaluation of biopsies of affected tissue can confirm the diagnosis.

CMV causes encephalitis of 2 types in patients with AIDS. The first type is difficult to differentiate clinically from HIV dementia. The disease is subacute or chronic, with symptoms of confusion and disorientation attributable to cortical involvement. Focal signs can be attributed to lesions in the brainstem. The second type presents with deficits in cranial nerves, nystagmus, and increasing ventricular size, which progresses rapidly to a fatal outcome.[56] CMV PCR of cerebrospinal fluid can be used to diagnose this condition.

CMV also causes polyradiculopathy. Patients subacutely present with weakness of legs and numbness, progressing to flaccid paraparesis, often with pain in the legs and perineum, bladder dysfunction, or both. The cerebrospinal fluid shows a remarkable preponderance of polymorphonuclear leukocytes.

**Drug regimens**

**Dosage**

**Ganciclovir**

The usual therapeutic and prophylactic dose of ganciclovir is 10 mg/kg/d, given by intravenous infusion twice a day for 2 to 3 weeks. For continued suppressive therapy to prevent relapse of infection (eg, in patients with AIDS) or long-term prophylaxis, either of the following may be used: (1) 5 mg/kg as a single daily dose each day of the week or (2) 6 mg/kg administered 5 days a week. Prophylactic oral ganciclovir (1,000 mg 3 times daily) recently was shown to significantly reduce the risk of CMV disease among persons with advanced AIDS.[59] The oral prodrug valganciclovir recently was approved for the treatment of CMV retinitis in patients with AIDS, with
900 mg being administered orally twice daily with food for 21 days as induction therapy, followed by a maintenance dose of 900 mg once daily with food.

**Foscarnet**

The usual dosage regimen of foscarnet for CMV infection is 180 mg/kg/d in 3 divided doses for 14 to 21 days, followed by a daily maintenance dose of 90 to 120 mg/kg.

**Cidofovir**

The recommended induction dose of cidofovir for patients with a serum creatinine level of 1.5 mg/dL or less, a calculated creatinine clearance greater than 55 mL per minute, and a urine protein level less than 100 mg/dL (equivalent to <2 plus proteinuria) is 5 mg/kg body weight administered once weekly for 2 consecutive weeks. The recommended maintenance dose of cidofovir is 5 mg/kg body weight administered once every 2 weeks.

**Efficacy**

**Ganciclovir**

Ganciclovir is indicated for the treatment and the prevention of life-threatening and sight-threatening CMV infections occurring in immunosuppressed patients. It is approved in the United States for the treatment and the suppression of retinitis caused by CMV in immunocompromised patients and for prevention of CMV disease in transplant recipients but frequently is used for a number of other serious CMV infections. Almost 90 percent of patients with CMV retinitis improve or stabilize their ocular disease and have significant reductions in viral titers from urine, blood, and throat after 1 to 2 weeks of ganciclovir therapy. [60] Because relapse of retinitis is virtually inevitable among patients with AIDS, ganciclovir should be continued chronically for CMV suppression after induction therapy. Patients who fail ganciclovir therapy may benefit from treatment with a combination of foscarnet and ganciclovir. [61] Patients with AIDS who have central nervous system disease caused by CMV also have been treated successfully with a combination of ganciclovir and foscarnet. [62] Up to one-quarter of ganciclovir recipients will develop resistance within 9 months of initiation of therapy. [63 and 64]

Patients with AIDS and solid organ transplant recipients who have gastrointestinal disease attributed to CMV appear to benefit from ganciclovir therapy. [65 and 66] Ganciclovir monotherapy does not appear to benefit bone marrow transplant recipients with CMV gastrointestinal infections. [67]

Limited and uncontrolled data suggest that ganciclovir therapy may be useful for patients with AIDS and CMV pneumonia. [24] By contrast, bone marrow transplant recipients with CMV pneumonia fail to respond to ganciclovir therapy alone [68] but may benefit from therapy with intravenous CMV hyperimmunoglobulin and ganciclovir given together. [69 and 70]

Ganciclovir has been evaluated in the treatment of neonates congenitally infected with CMV. In a recently completed phase III randomized controlled trial, ganciclovir therapy (6 mg/kg per dose administered twice daily for 6 weeks) protected infants from hearing deterioration beyond 1 year of life. [71] Transient effects on growth also were seen, as was a decreased time to resolution of transaminase elevation. However, approximately two-thirds of treated patients developed neutropenia, with one-half of them requiring dose modification.

Ganciclovir is useful for prevention of CMV infections in high-risk immunocompromised subjects, including bone marrow and solid organ transplant recipients. Strategies that have been used to reduce the frequency of disease
after transplantation include routine administration of ganciclovir to all at-risk transplant recipients and preemptive administration to those who have a positive culture for CMV after undergoing transplantation. Preemptive therapy has been demonstrated to effectively reduce CMV disease in liver transplant recipients,[72] lung transplant recipients, [73] heart transplant recipients, [74] and bone marrow transplant recipients. [75, 76 and 77] CMV-seropositive heart, lung, or liver transplant recipients who receive routine prophylaxis with ganciclovir for 1 month also have significant reductions in CMV infection and disease after transplant. [78, 79, 80, 81 and 82] Preemptive administration of ganciclovir improves survival among bone marrow transplant recipients, [83 and 84] but routine initiation of prophylactic ganciclovir prior to bone marrow transplantation in patients who are CMV-seropositive does not impact survival. [84 and 85] Ultimately, however, the best way to prevent primary CMV infections among seronegative solid organ transplant recipients who receive an organ from a CMV-seropositive donor has yet to be determined.

**Foscarnet**

The most important indication for foscarnet is for therapy of sight-threatening chorioretinitis caused by CMV in patients with AIDS.[33] Several controlled trials have demonstrated that foscarnet is as effective as ganciclovir in managing this infection and may even offer a survival advantage because of its inherent activity against HIV. [86] Approximately 90 percent of patients have stabilization of their retinitis, and time to progression of infection is prolonged to approximately 3 months. [87]

**Cidofovir**

Cidofovir has been evaluated for the treatment of CMV retinitis in patients with AIDS in 3 separate studies,[88 and 89] and in each trial it delayed retinal disease progression. Cidofovir also has been used successfully in the treatment of disease caused by acyclovir-resistant HSV isolates. [90]

**Adverse effects**

**Ganciclovir**

The most important toxic effect of ganciclovir is myelosuppression. Dose-related neutropenia, defined as more than a 50 percent decrease in absolute neutrophil count from baseline or less than 1,000 per µL, is the most consistent hematologic disturbance.[24] The incidence of neutropenia is approximately 40 percent. It is dose limiting in approximately 15 percent of courses and is reversible on cessation of drug. [24] The likelihood of neutropenia occurring after oral administration of ganciclovir is lower, with 14 to 24 percent of patients developing an absolute neutrophil count of less than 1,000 per µL. [91] Hematopoietic growth factors may be useful in preventing or in counteracting neutropenia. [60] Thrombocytopenia (≤ 50,000 platelets per µL) occurs in approximately 20 percent of treated patients. Anemia occurs in only approximately 2 percent of ganciclovir recipients.

Approximately 5 percent of ganciclovir recipients experience some combination of headache, confusion, altered mental status, hallucinations, nightmares, anxiety, ataxia, tremors, and seizures. Approximately 2 percent develop fever, rash, and abnormal levels of serum hepatic enzymes. Intraocular injection of ganciclovir can cause transient increases in intraocular pressure, with associated intense pain and amaurosis lasting up to 30 minutes.[92]

In preclinical test systems, ganciclovir is mutagenic, carcinogenic, and teratogenic. Additionally, it causes irreversible reproductive toxicity in animal models.[93]
Foscarnet

The most common and serious adverse effects of foscarnet therapy are nephrotoxicity and metabolic derangements. Azotemia, proteinuria, acute tubular necrosis, crystalluria, and interstitial nephritis can occur,[86] and serum creatinine concentrations increase in up to 50 percent of patients, usually during the second week of therapy. In most affected patients, renal function returns to normal within 2 to 4 weeks of stopping therapy. Risk factors for developing renal dysfunction include preexisting renal disease, concurrent use of other nephrotoxic drugs, dehydration, rapid injection of large doses, and continuous intravenous infusion of drug. [94] Electrolyte disturbances, including symptomatic hypocalcemia and hypercalcemia and hypophosphatemia and hyperphosphatemia, can be caused by foscarnet therapy. Metabolic disturbances can be minimized if foscarnet is administered by slow infusion, with rates not exceeding 1 mg/kg per minute. Common central nervous system symptoms associated with foscarnet therapy are headache, tremor, irritability, seizures, and hallucinations. Fever, nausea, vomiting, abnormal serum hepatic enzymes, anemia, granulocytopenia, and genital ulcerations also have been reported. Concomitant use of amphotericin B, cyclosporine, gentamicin, and other nephrotoxic drugs increases the likelihood of renal dysfunction associated with foscarnet therapy.

Cidofovir

The principle adverse event associated with systemic administration of cidofovir is nephrotoxicity.[49 and 50] Cidofovir concentrates in renal cells in amounts 100 times greater than is seen in other tissues, producing severe proximal convoluted tubule nephrotoxicity when concomitant hydration and administration of probenecid are not used. [50] When present, renal toxicity manifests as protein-uria and glycosuria. [95] To decrease the potential for nephrotoxicity, aggressive intravenous prehydration and coadministration of probenecid are required with each cidofovir dose. Cidofovir should not be administered concomitantly with other nephrotoxic agents. It is contraindicated in patients with a serum creatinine level greater than 1.5 mg/dL, a calculated creatinine clearance of 55 mL per minute or less, or a urine protein count of 100 mg/dL or greater (equivalent to 2 plus proteinuria). The maintenance dose of cidofovir must be reduced from 5 mg/kg to 3 mg/kg for an increase in serum creatinine of 0.3 to 0.4 mg/dL above baseline. Cidofovir therapy must be discontinued if the serum creatinine level increases to 0.5 mg/dL or more above baseline. In animal studies, cidofovir is carcinogenic and teratogenic and causes hyposperma.

Resistance

Ganciclovir

Resistant strains of CMV should be suspected when progressive disease and continued recovery of virus occurs despite ganciclovir therapy. In 1 study, 8 percent of 72 patients with AIDS had progressive infection associated with isolation of ganciclovir-resistant strains of CMV after 3 months of continuous ganciclovir therapy.[96] Resistance may be more likely to occur in patients treated with oral ganciclovir as compared with intravenous ganciclovir, possibly because of the selective pressure applied by the lower concentrations of drug achieved with oral administration. [97] By contrast, CMV isolates from solid organ transplant recipients who have been exposed to ganciclovir appear less likely to develop resistance to the drug. [98] Foscarnet may be useful in the therapy of CMV infections caused by ganciclovir-resistant isolates. [99]

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* ✉ Corresponding author. Address correspondence to David W. Kimberlin, MD, Assistant Professor of Pediatrics, The University of Alabama at Birmingham, Division of Pediatric Infectious Diseases, 1600 Seventh Ave S, Suite 616, Birmingham, AL 35233;

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