70% of those given ganciclovir); inclusion bodies disappeared from biopsies in 55% and 50%, respectively; and symptoms improved equally as well (82% vs. 80%, respectively). Adverse events were qualitatively different, but quantitatively and clinically equivalent, in the two groups. The authors concluded ganciclovir and foscarnet were equally safe and effective for treatment of CMV esophagitis in patients with AIDS (Parente and Bianchi Porro, 1998).

Combination therapy of CMV infections with ganciclovir and foscarnet was evaluated in an open, prospective trial in patients with gastrointestinal infection ($N = 7$) or retinitis ($N = 7$). Five of the patients with gastrointestinal infections had a remission, as did 5 of those with retinitis. No new toxicities were seen with the combination (Salberger *et al.*, 1994). However, as noted by Drew (2006), there is no substantive evidence that combination therapy is better than monotherapy.

NEUROLOGIC DISEASE

Anduze-Faris *et al.* (2000) conducted an open, noncomparative study of combined foscarnet and ganciclovir for neurologic disease in HIV-infected subjects before the era of highly active combination antiretroviral therapy. A total of 31 patients with CMV encephalitis or myelitis were given foscarnet 90 mg/kg and ganciclovir 5 mg/kg i.v. twice daily for 3–6 weeks followed by maintenance therapy at the same doses once daily. Of the 31 patients treated, 23 (74%) responded during the induction phase by improvement or stabilization of disease and were put on maintenance therapy. During the maintenance phase, CMV disease progressed in 10 patients, with a median time to relapse of about 4 months. Note that 10 patients had at least one drug discontinued during the induction phase because of toxicity.

An HIV-infected patient who developed CMV polyradiculitis while receiving ganciclovir did not respond to therapy with foscarnet (de Gans *et al.*, 1990), although there are other case reports of foscarnet being used with success for that condition (Manji *et al.*, 1992; Domingo *et al.*, 1994; Corral *et al.*, 1996). CMV ventriculoencephalitis has also been reported to respond poorly to foscarnet (Salazar *et al.*, 1995), although this may in part relate to difficulty in making the diagnosis, thus delaying specific therapy until late in the course of the disease. In two case reports of patients with CMV encephalitis that was refractory to ganciclovir alone, the patients received a 3- to 6-week combination of foscarnet and ganciclovir with documented success (Enting *et al.*, 1992; Peters *et al.*, 1992). Combination therapy with ganciclovir and foscarnet for CMV polyradiculomyelitis has also been reported (Karmochkine *et al.*, 1994).

7b. Preventive or Preemptive Treatment of CMV infection in patients with immunosuppression not related to HIV infection

PREVENTATIVE TREATMENT

Ample clinical data support the efficacy of foscarnet for prevention of CMV viremia in patients with iatrogenic immunodeficiency. However, in general, most authorities recommend initiating treatment with ganciclovir or valganciclovir, and using foscarnet only for patients who cannot tolerate that drug or for patients with ganciclovir-resistant CMV infections (Bueno *et al.*, 2002). The International Herpes Management Forum has issued guidelines for the diagnosis and management of CMV infections in solid organ and stem cell transplant recipients (Razonable and Emery, 2004). The investigational drug letermovir has been shown to be active for this indication (Chemaly *et al.,* 2014), and it may well be widely used if it is generally approved by regulatory agencies.

Foscarnet has been shown to prevent CMV infection in seropositive bone marrow transplant recipients. In one trial, patients received intermittent intravenous foscarnet at a dose of 40 mg/kg every 8 hours from 7 days before to 30 days after transplant, then 60 mg/kg/day for another 45 days. No patient developed CMV disease (Reusser *et al.*, 1992). This finding was supported by another study in which foscarnet lowered the risk of CMV infection compared with historic controls (Bacigalupo *et al.*, 1994a).

Ippoliti *et al.* (1997) gave prophylactic foscarnet (60 mg/kg once daily) to 39 adults who had received a bone marrow transplant and were unable to tolerate ganciclovir because of either prior ganciclovir-induced neutropenia or delayed engraftment. Foscarnet was continued until the contraindications to ganciclovir therapy had resolved, and ganciclovir prophylaxis was then resumed. Foscarnet was well tolerated, but 6 (15%) of the patients given foscarnet prophylactically had detectable CMV infection and the overall mortality was 5%. The authors concluded that foscarnet administration was a safe and effective method for preventing CMV infections in this group of patients (Ippoliti *et al.*, 1997).

Shereck *et al.* (2007) studied alternate-day foscarnet–ganciclovir prophylaxis of CMV infections in 53 children and adolescents receiving allogeneic stem cell transplants who were at risk for CMV infections because either donors or the patients were CMV seropositive. None of the patients developed CMV disease, 5% had hematologic toxicity requiring discontinuation of ganciclovir, and 25% required discontinuation of foscarnet because of electrolyte abnormalities or nephrotoxicity.

Bregante and colleagues (2000) conducted a dose-finding study of foscarnet prophylaxis of CMV infections after allogenic bone marrow transplantation. Foscarnet was given in a complex dosing scheme, a high dose during induction for 1 month and then a further 2 months of maintenance therapy. There was a clear dose–response relationship in terms of prevention of CMV antigenemia (see Table 219.12). Increased serum creatinine was seen in 15 patients, and in 9 the drug had to be discontinued. Renal dysfunction resolved in all patients when foscarnet was discontinued.

PREEMPTIVE TREATMENT OF CMV INFECTION IN TRANSPLANT RECIPIENTS

Much clinical data support the efficacy of foscarnet for preemptive treatment of CMV viremia (treatment on evidence of CMV viremia before clinical disease occurs) in patients with iatrogenic immunocomprimise. General recommendations