treatment of CMV retinitis in patients with AIDS, as monotherapy, and in combination with ganciclovir for patients who have relapsed after monotherapy with either drug. It is also approved for mucocutaneous infections in immunocompromised patients due to aciclovir-resistant strains of HSV. Both of these indications are supported by excellent clinical data.

In most centers, ganciclovir or valganciclovir (see Chapter 215, Ganciclovir and valganciclovir) would be the drug of first choice for the treatment of CMV infections, regardless of the patient population, with foscarnet being reserved for patients who are intolerant of ganciclovir or who have developed ganciclovir resistance. The new drug letermovir (an investigational drug at this writing; see Chapter 220, Letermovir) has been shown to prevent CMV disease (Chemaly *et al.,* 2014), and further studies may well document a therapeutic role in the future. Likewise, foscarnet therapy is almost exclusively used for infections by aciclovir-resistant HSV and VZV, with good data supporting its efficacy, and it has been used successfully for treatment of drug-resistant strains of HHV-6, likewise in small studies or case reports. Foscarnet is virtually never used for treatment of HIV or hepatitis B virus infections because it makes little sense to treat an incurable, systemic infection with a toxic drug that can be delivered only intravenously, although it has been shown to be active against those viruses *in vivo*.

Topical foscarnet (on the skin, or on the cornea of the eye or by intravitreal administration) is now very rarely used for treating infection by any herpesvirus. The evidence for efficacy of topical therapy compared with systemic therapy is fair at best. For HSV keratitis, foscarnet's efficacy is equivalent to trifluridine, aciclovir, and ganciclovir (Wilhelmus, 2015).

7a. Treatment of CMV infections in HIV-infected patients

In HIV-infected patients, foscarnet is generally effective therapy for CMV infections of all tissues and organs, including the eye, gastrointestinal tract (esophagitis, duodenitis, pancreatitis, and colitis), and the nervous system (encephalitis, myelitis). The efficacy of foscarnet for these indications was established preliminarily in a ground-breaking phase II open-label study in HIV-infected subjects with CMV viremia showing that a 14-day course of foscarnet (100 mg/kg every 12 hours) reduced or eliminated CMV markers in the blood (Salmon-Ceron *et al.*, 1999). To some extent this could be considered a preemptive therapeutic strategy because achieving a negative blood culture during foscarnet therapy reduced the subsequent risk of CMV disease (odds risk [OR]: 2.64; $p = 0.02$).

CMV RETINITIS

In untreated patients with advanced HIV infection, CMV retinitis will usually progress rapidly, with a mean time to progression of 22 days (see Figure 219.3) and a range of 2–6 weeks (Palestine *et al.*, 1991). Retinitis in patients with positive blood or urine cultures for CMV progresses more rapidly than those with negative cultures (Anonymous, 1997). Therapy with foscarnet, given either as 60 mg/kg every 8 hours or as a continuous infusion of 230 mg/kg daily after an initial bolus, results in clinical responses that are evident as early as the third day of therapy (Walmsley *et al.*, 1988; Katlama *et al.*, 1992). In patients with CD4 lymphocyte counts < 100/μl, relapse will almost always occur without maintenance therapy often within a month of cessation of therapy (Walmsley *et al.*, 1988). Patients who achieve a sustained rise in CD4 counts to ≥ 100/μl as the result of antiretroviral therapy, may not need maintenance therapy (Waib *et al.*, 2007). When treated with 60 mg/kg every 8 hours for 2–3 weeks followed by maintenance therapy of 90 mg/kg daily, the mean time to progression in patients with CD4 counts < 100/μl ranges from 6.7 to 13.3 weeks (Palestine *et al.*, 1991; Jacobson 1992a; Jacobson 1992b; see Figure 219.3). Patients who fail foscarnet therapy rarely have foscarnet-resistant strains of CMV (Anonymous, 1997).

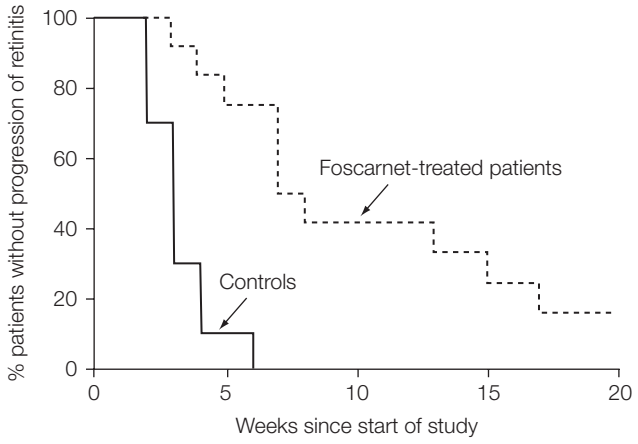

Figure 219.3. Progression of CMV retinitis over time in patients receiving immediate foscarnet treatment or no (delayed) treatment. (Reproduced with permission from Palestine *et al.* (1991).)

Compared with ganciclovir (see Chapter 215, Ganciclovir and valganciclovir) for the treatment of CMV retinitis, foscarnet has certain advantages and disadvantages. The Study for the Ocular Complications of AIDS, a multicenter, randomized comparative trial of ganciclovir versus foscarnet undertaken in the era before potent combination antiretroviral therapy, found that both drugs had similar efficacy and were associated with similar times to progression of retinitis. However, there was a survival advantage for patients randomized to receive foscarnet (Anonymous, 1992; Anonymous 1994; see Figure 219.4). These findings were confirmed in a separate study (Polis *et al.*, 1993) and may possibly be explained by the established antiretroviral activity of foscarnet *in vivo*, compared with ganciclovir, which has none (Jacobson *et al.*, 1988; Fletcher *et al.*, 1994; Kaiser *et al.*, 1995; Anonymous 1995a), and *in vitro* (Sandstrom *et al.*, 1985; Sarin *et al.*, 1985). However, a subsequent study of 279 patients with persistently active or relapsed retinitis found no survival advantage of foscarnet over ganciclovir or the over the combination of both drugs (Anonymous, 1996). It is unlikely that the antiretroviral and life-prolonging effects of foscarnet would be significant in the current population of HIV-infected