respectively) (Anonymous, 19924). The benefits of foscarnet in that study were probably due to its effect on HIV infection, and those benefits would not be relevant in the current era when such patients are on combination antiretroviral therapy. The SOCA study was one of the first to measure clinical progression based on funduscopic photographs assessed by independent investigators. In another study, patients treated with GCV initially responded faster than those treated with foscarnet, but the eventual rates of response did not differ (Moyle *et al.*, 1992).

In the era before effective combination antiretroviral therapy became widely available (i.e. before about 1995), there was a debate as to whether patients with peripheral, non-sight-threatening CMV retinitis would benefit from GCV therapy, and the debate continued until a clinical trial was designed to specifically address this question. Spector *et al.* (1993) found that patients with peripheral retinitis who were randomized to receive immediate therapy with intravenous GCV 5 mg/kg twice daily for 14 days followed by maintenance therapy of 5 mg/kg daily had a median time to progression of 49.5 days compared with only 13.5 days in the group whose therapy was deferred until their disease progressed (see Figure 215.2). This study also used independent assessments of fundus photography to determine time to progression. Thus all patients with HIV-related CMV retinitis, regardless of whether the lesions are peripheral or central, should be offered therapy. The median progression rates for patients receiving GCV is 11.5 μm of retinal progression per day (range 0–25 μm) while that for untreated patients is 24 μm (range 0–164 μm) per day (Holland and Schuler, 1992). Nevertheless, in resource-limited settings where combination antiretroviral therapy is available to patients and VGCV is not, it is still an open question as to whether intravitreal GCV therapy is necessary or beneficial for patients whose CMV retinitis is limited to the peripheral retina, who can immediately initiate antiretroviral therapy after retinitis is diagnosed, and in whom immune reconstitution may make such invasive treatment unnecessary. On the other hand, in April 2015, VGCV was included in the 19th World Health Organization Model list of essential medications because even with local intravitreal GCV therapy, the short-term mortality associated with HIV-related CMV retinitis in resource-limited settings (28%) is comparable to that associated with HIV-related disseminated cryptococcal infection (Tun *et al.*, 2014).

Combination therapy using both GCV and foscarnet has been evaluated in a multicenter randomized controlled trial among patients who had persistently active CMV retinitis or whose retinitis had relapsed on therapy. By funduscopic photography, combination therapy was found to be the more effective therapy for controlling retinitis than a strategy of reinduction with high dose GCV or foscarnet with median times to progression of 4.3 months versus 1.3 and 2.0 months (Anonymous, 1996). Combination foscarnet and GCV therapy is well tolerated, with no significant increase in renal, bone marrow, or other toxicity. Foscarnet alone or in combination with GCV has proved useful for patients with clinically resistant retinitis who have laboratory evidence of GCV resistance (Flores-Aguilar *et al.*, 1993). In a small phase I study, combining CMV immunoglobulin with GCV did not improve the efficacy of that drug for treatment of CMV retinitis in patients with AIDS (Jacobson *et al.*, 1990).There have been several reports of infants and children with CMV retinitis who responded favorably to GCV therapy (Salvador *et al.*, 1993; Peters *et al.*, 1995). Combination therapy using GCV and foscarnet in a child with HIV-related CMV retinitis unresponsive to monotherapy with either drug has also been reported to be effective (Butler *et al.*, 1992).

Intravitreal injection of GCV has been used in patients intolerant of or having no access to GCV. In an early study by Heinemann (1989), stabilization of retinitis occurred in all of 7 patients treated with intravitreal injections of GCV (1200 μg in six divided doses) as induction therapy followed by 200 μg/week maintenance therapy. Success with this approach was observed in another study, in which treatment of 44 patients with unilateral CMV retinitis (55%) or bilateral disease (45%) using intravitreal GCV at a dose of 400 μg per injection led to healing after a mean of 6.6 (range 4–14) injections per eye. After 8 weeks of maintenance therapy (1 injection per week) the relapse rate was 53%. Involvement of the other eye occurred in 11% and systemic disease in 16% of patients (Cochereau-Massin *et al.*, 1991). Suppression of retinitis in 78% of treated eyes after intravitreal administration of GCV has also been reported in patients who were unable to tolerate intravenous GCV or who had retinitis unresponsive to intravenous GCV

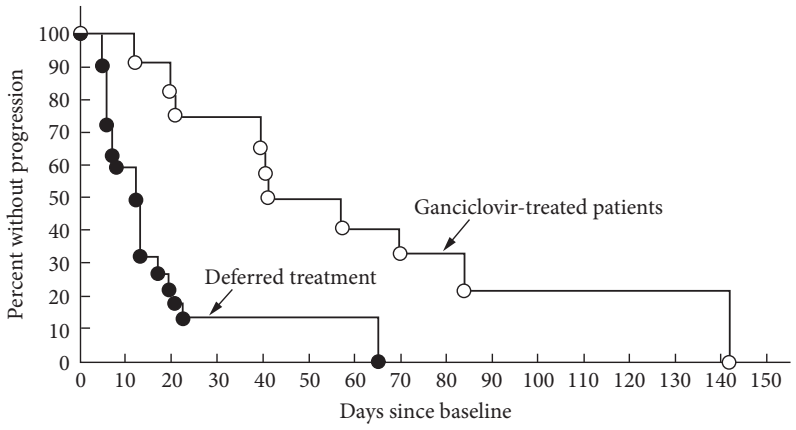

Figure 215.2. Kaplan–Meier estimates of the proportion of patients with progression of retinitis when given immediate versus deferred GCV therapy ($p = 0.001$ by the log-rank test). (Reproduced with permission from Spector *et al.* (l993).)