receiving combination antiretroviral therapy, were included in the study if they had a CD4 count < 100 cells/μl, HIV viral load > 400 copies/ml, and were CMV seropositive without evidence of end-organ disease. Following enrollment, patients were screened for CMV viremia, and if positive, they were randomized to receive oral VGCV (900 mg twice a day for 3 weeks, followed by 900 mg daily) or placebo. Of 338 patients enrolled, 68 developed viremia, and 47 were randomized (24 to VGCV and 23 to placebo). Among the viremic subjects randomized to VGCV or placebo, median absolute CD4 count was 12 cells/μl, and 79.7% reported they were currently taking antiretroviral therapy. A total of 10 subjects developed CMV end-organ disease, 4 in the VGCV group and 6 in the placebo group. A total of 15 patients died (7 in the VGCV group and 8 in the placebo group); no deaths were considered directly associated with CMV. Due to the low incidence of disease, there was insufficient power to detect a significant difference between the groups; and the authors concluded that preemptive treatment does not appear to benefit patients with persistently low CD4 cell counts. Two subsequent single-center retrospective studies have evaluated the impact of preemptive treatment in similar populations, but they have had mixed results. The study conducted by Mizushima *et al.*, (2013) included 126 HIV-infected, treatment-naive patients with CMV viremia. Of those, 30 received preemptive CMV treatment (regimens were determined by clinician preference, but the majority received GCV i.v.). CMV end-organ disease was diagnosed in statistically significantly fewer patients receiving preemptive treatment than those not receiving it (31% vs. 10%; hazard ratio [HR]: 0.286; 95% confidence interval [CI]: 0.087–0.939; $p = 0.039$). No difference in mortality was observed between the two groups. Mattioni *et al.* (2015) reviewed the outcomes of 71 HIV-infected patients with documented CMV viremia but no end-organ disease. Of those, 16 received preemptive treatment (regimen based on prescriber preference, but most received VGCV). When adjusted for baseline CD4 count and CMV viral load, there was an insignificant trend toward reduced risk of the composite outcome of CMV end-organ disease and death (HR: 0.25; $p = 0.13$). Patients receiving preemptive treatment experienced substantial drug toxicities, most commonly neutropenia and anemia.

7b. Cytomegalovirus infection in hematopoietic cell transplant recipients

CMV infection or reactivation can result in life-threatening disease in hematopoietic cell transplant (HCT) recipients, particularly in CMV-seronegative recipients who are given CMV-seropositive, T-cell-depleted, or HLA-mismatched bone marrow grafts or stem cells (Ljungman *et al.*, 1994; Milano *et al.*, 2011). Prevention of CMV infection in CMV-seronegative transplantation patients is possible by use of seronegative donors and leuko-depleted blood products (Zaia, 1993).

PROPHYLAXIS VERSUS PREEMPTIVE THERAPY

Most transplant centers limit a prophylactic antiviral approach (i.e., initiating GCV or VGCV in HCT recipients before transplantation or at the time of engraftment) to patients at very high risk for opportunistic CMV disease and apply a preemptive antiviral treatment approach, in which patients are monitored frequently for CMV DNA or CMV pp65 antigen in blood after transplantation, and treat only those who become viremic with GCV or VGCV. Detailed international consensus guidelines for each approach have been developed by a panel of clinical experts (Tomblyn *et al.*, 2009), but there is no consensus on which is the most appropriate approach for specific patients.

A series of trials conducted in the 1990s demonstrated the efficacy of the prophylactic approach in the HCT setting. In one regimen, prophylactic treatment of CMV-seropositive patients with intravenous GCV (2.5 mg/kg every 8 hours) for 7 days before transplantation and then 6 mg/kg daily for 5 days/week after transplantation significantly reduced CMV infection (defined as a positive viral culture, seroconversion, or positive histologic findings), which occurred in 8 of 40 (20%) in treated patients versus 25 of 45 (56%) of placebo recipients ($p < 0.001$). There was also a trend toward a lower rate of CMV disease in the prophylaxis group (Winston *et al.*, 1993). Using a similar approach, GCV prophylactic treatment given before transplantation at a dose of 6 mg/kg to CMV-seropositive recipients and after transplantation to HCT recipients who were seropositive or who had received a transplant from a seropositive donor, was found to markedly reduce the rate of symptomatic CMV infection. Only 1 of 40 (2.5%) GCV recipients developed symptoms, compared with untreated historical controls, in whom 23 of 39 (59%) developed symptomatic disease (von Bueltzingsloewen *et al.*, 1993). In another approach, GCV prophylaxis administered after transplantation was superior to placebo in preventing the development of positive CMV cultures (3% vs. 45%, respectively) and disease (0% vs. 29%, respectively) during the first 100 days posttransplant (Goodrich *et al.*, 1993).

While no randomized trials have been published comparing oral VGCV to intravenous GCV in HCT recipients, logic (because VGCV is converted to GCV at concentrations equivalent to intravenous administration) and several uncontrolled studies suggest similar efficacy in preventing CMV infection or disease (Ayala *et al.*, 2006; Busca *et al.*, 2007; van der Heiden *et al.*, 2006). Independent of the presence of intestinal graft-versus-host disease complicating HCT, the AUC of GCV after standard VGCV dosing to HCT patients is greater than that after standard intravenous GCV dosing; however, there appears to be no increase in toxicity with VGCV compared to intravenous GCV (Einsele *et al.*, 2006).

Although prophylactic therapy significantly reduced the risk of early CMV disease in this patient population, reactivation was commonly seen after cessation of prophylaxis within 1 year after transplantation, suggesting that T-lymphocyte-mediated responses to this virus are still suppressed (Li *et al.*, 1994). Because the hematologic toxicity of prolonged GCV therapy and the development of more rapid and sensitive diagnostic techniques (detection of CMV pp65 antigenemia and detection of CMV DNA by PCR amplification) for detecting reactivated CMV infection (Boeckh *et al.*, 2004; Allice *et al.*, 2008; Gerna *et al.*, 2008), a preemptive approach to preventing CMV disease began to be favored.