hepatitis B virus replication in a patient with a severe recurrence of that infection after liver transplantation (Angus *et al.*, 1993). This report was followed by a pilot study involving nine patients with post-transplant hepatitis B infection who were treated with GCV for 3–10 months. Hepatitis B virus replication was reduced, as assessed by serum and hepatic hepatitis B virus DNA levels, and serum alanine aminotransferase levels declined (Gish *et al.*, 1996).

7g. Solid tumor-targeted gene therapy

Gene therapy using cells transfected with a so-called suicide gene followed by treatment with GCV is an area of active investigation in oncology. The principle is to make tumor cells susceptible to chemotherapy by transfecting them with a gene that activates a cytocidal drug. GCV has almost no effect on normal cells because they lack the enzyme required for its initial phosphorylation step (monophosphorylation; subsequent phosphorylation steps to the triphosphate are mediated by normal cellular enzymes), and only GCV triphosphate is cytotoxic. Transfection of the herpes simplex TK gene into tumor cells by an adenovirus vector makes the cells susceptible to GCV, as the TK initiates the phosphorylation cascade; subsequent treatment with intravenous GCV selectively kills the TK-expressing tumor cells. This strategy is being investigated for the treatment of pleural mesothelioma, glioblastoma multiforme, and prostatic cancer. A total of 21 patients with pleural mesothelioma received a high dose of an adenovirus encoding the HSV TK followed by intravenous GCV. Posttreatment antibodies to the adenovirus were noted in a majority of patients, but two patients with long-term followup were noted to have had a clinical response (Sterman *et al.*, 2005). In an early phase I/II study, patients with progressive or recurrent glioblastoma multiforme received the HSV TK vector followed by intravenous GCV. Although a clinical response was noted, approximately half the patients experienced serious adverse events, possibly related to the treatment modality (Prados *et al.*, 2003). In a phase I study, the adenovirus vector was directly injected into the tumor of patients with prostatic cancer that locally recurred after hormonal therapy. Of these, 5 patients had a decrease in the serum concentration of prostate-specific antigen (PSA), and 1 patient had a prolonged clinical response. In addition, the authors describe a significant prolongation of the median PSA doubling time (an indication of slowed tumor growth) from 2.9 to 6.2 months (Nasu *et al.*, 2007). More recently, tumor-specific *Salmonella* engineered to carry TK was demonstrated to effectively treat human lymphoma xenografts when co-administered intratumorally or intravenously with GCV in mice lacking a functional adaptive immune system (Massa *et al.*, 2013). A review of this topic is available (Karjoo *et al.*, 2016).

Acknowledgment: The previous version of this chapter, published in the 6th edition of *Kucers' The Use of Antibiotics*, was co-authored by Ian R. McNicholl of San Francisco General Hospital, San Francisco, CA, USA. His contribution was substantial and much appreciated.

REFERENCES

Acosta EP, Brundage RC, King JR *et al.* (2007). Ganciclovir population pharmacokinetics in neonates following intravenous administration of ganciclovir and oral administration of a liquid valganciclovir formulation. *Clin Pharmacol Ther* **81**: 867.

Agarwal A, Kumari N, Trchan A *et al.* (2014). Outcome of cytomegalovirus retinitis in immunocompromised patients without human immunodeficiency virus treated with intravitreal ganciclovir injection. *Graefes Arch Clin Exp Ophthalmol* **252**: 1393.

Agut H, Huraux JM, Collandre H, Montagnier L (1989). Susceptibility of human herpesvirus 6 to aciclovir and ganciclovir. *Lancet* **2**: 626.

AIDS*info* (nd). Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. aidsinfo.nih.gov /guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment -guidelines/0. Accessed 5 January 2017.

Akesson-Johansson A, Harmenberg J, Wahren B, Linde A (1990). Inhibition of human herpesvirus 6 replication by 9-[4-hydroxy-2-(hydroxymethyl) butyl] guanine (2HM-HBG) and other antiviral compounds. *Antimicrob Agents Chemother* **34**: 2417.

Akula SK, Ma PE, Reyman GA *et al.* (1994). Treatment of cytomegalovirus retinitis with intravitreal injection of liposome encapsulated ganciclovir in a patient with AIDS. *Br J Ophthalmol* **78**: 677.

Allice T, Cerutti F, Pittaluga F *et al.* (2008). Evaluation of a novel real-time PCR system for cytomegalovirus DNA quantitation on whole blood and correlation with pp65-antigen test in guiding pre-emptive antiviral treatment. *J Virol Methods* **148**: 9.

Altman C, Bedossa P, Dussaix E, Buffet C (1995). Cytomegalovirus infection of esophagus in immunocompetent adults. *Dig Dis Sci* **40**: 606.

Amir J, Wolf DG, Levy I (2010). Treatment of symptomatic congenital cytomegalovirus infection with intravenous ganciclovir followed by long-term oral valganciclovir. *Eur J Pediatr* [ePub ahead of print].

Andrei G, Snoeck R, Schols D *et al.* (1991). Comparative activity of selected antiviral compounds against clinical isolates of human cytomegalovirus. *Eur J Clin Microbiol Infect Dis* **10**: 1026.

Anduze-Faris BM, Fillet AM, Gozlan J *et al.* (2000). Induction and maintenance therapy of cytomegalovirus central nervous system infection in HIV-infected patients. *AIDS* **14**: 517.

Angus P, Richards M, Bawden S *et al.* (1993). Combination antiviral therapy controls severe post-liver transplant recurrence of hepatitis B virus infection. *J Gastroenterol Hepatol* **8**: 353.

Anonymous (1996). Combination foscarnet and ganciclovir therapy vs monotherapy for the treatment of relapsed cytomegalovirus retinitis in patients with AIDS. Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group. *Arch Ophthalmol* **114**: 23.

Anonymous (1994). Foscarnet-ganciclovir cytomegalovirus retinitis trial. 4. Visual outcomes. Studies of ocular complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group. *Ophthalmology* **101**: 1250.

Anonymous (1995). Morbidity and toxic effects associated with ganciclovir or foscarnet therapy in a randomised cytomegalovirus retinitis trial. Studies of Ocular Complications of AIDS Research Group, in collaboration with the AIDS Clinical Trials Group. *Arch Intern Med* **155**: 65.

Anonymous (1992). Mortality in patients with acquired immune deficiency syndrome treated with either foscarnet or ganciclovir for cytomegalovirus retinitis. Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group. *N Engl J Med* **326**: 213.

Arabia FA, Rosado LJ, Huston CL *et al.* (1993). Incidence and recurrence of gastrointestinal cytomegalovirus infection in heart transplantation. *Ann Thorac Surg* **55**: 8.

Arevalo JF, Gonzalez C, Capparelli EV *et al.* (1995). Intravitreous and plasma concentrations of ganciclovir and foscarnet after intravenous therapy in patients with AIDS and cytomegalovirus retinitis. *J Infect Dis* **172**: 951.

Armitage JM, Kurland G, Michaels M *et al.* (1995). Critical issues in pediatric lung transplantation. *J Thorac Cardiovasc Surg* **109**: 60.