Chapter 8
Resistance of Herpesviruses to Antiviral Agents

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Acyclovir is the prototype of a series of antivirals which are effective against herpesviruses. However, resistance to this class of drugs can occur and is being seen mainly in immunocompromised patients with herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections. Clinical use of intravenous (IV) ganciclovir began in 1984 for the treatment of life-threatening and sight-threatening human cytomegalovirus (HCMV) infections in immunocompromised patients. A few years later, description of ganciclovir-resistant HCMV strains were reported in AIDS patients with HCMV retinitis and, more recently, in organ or bone marrow transplant recipients. Foscarnet and cidofovir became available subsequently and resistance to these agents has also been described.

In this chapter we review the available antiviral drugs for HCMV, HSV and VZV, the methods for detecting antiviral resistance, the clinical significance of resistant strains and their treatment.

8.1 Antiviral Agents for Herpesvirus Infections

Three antiviral agents and a prodrug are currently available for the systemic treatment of HCMV infections. Ganciclovir (GCV, Cytovene, Hoffmann LaRoche) is a deoxyguanosine analog and was the first drug to be approved in 1988. Since then, it has remained the first line treatment for HCMV infections in immunocompromised patients. Upon entry in HCMV-infected cells, GCV is selectively phosphorylated by a viral protein kinase homolog (the product of the UL97 gene, pUL97). Subsequently, cellular kinases convert GCV-monophosphate into GCV-triphosphate, which acts as a potent inhibitor of the HCMV DNA polymerase (pol) by competing with deoxyguanosine triphosphate on the enzyme-binding site (Figure 8.1). Ganciclovir is also incorporated into the viral DNA where it slows down and eventually stops chain elongation (Balfour, 1999; Biron et al., 1985; Sullivan et al., 1992). Ganciclovir formulations are available for intravenous (IV) or oral administration and as ocular implants for the local treatment of HCMV retinitis. Due to its poor bioavailability (~6%), efforts were made to develop prodrugs of GCV. Valganciclovir (VGCV, Valcyte, Hoffmann LaRoche) is a new valyl ester formulation of
Fig. 8.1 Mechanisms of action of antiviral agents used in the treatment of herpesvirus infections. TK, thymidine kinase; ANP, acyclic nucleoside phosphonate.

GCV exhibiting about 10 times the bioavailability of GCV following oral administration (Pescovitz et al., 2000).

The other two compounds approved for systemic treatment of HCMV infections are also potent inhibitors of the viral DNA pol. However, due to their toxicity profiles, they are usually reserved for patients failing or not tolerating GCV therapy. Cidofovir (CDV, Vistide, Gilead Sciences) is a nucleotide analog of cytidine (also called acyclic nucleoside phosphonate) that only requires activation (phosphorylation) by cellular enzymes to exert its antiviral activity (Cihlar and Chen, 1996). Once in its diphosphate form, CDV inhibits the HCMV DNA pol by a mechanism similar to that of GCV (Figure 8.1). Foscarnet (FOS, Foscavir, Astra-Zeneca), a pyrophosphate analog, differs from the two previous antivirals both by its mechanism of action and by the fact that it does not require any activation step to exert its antiviral activity. Foscarnet binds to and blocks the pyrophosphate binding site on the viral polymerase, thus preventing incorporation of incoming dNTPs into viral DNA (Figure 8.1) (Chrisp and Clissold, 1991). Finally, formivirsen (Vitravene, Novartis) is a 21-nt long antisense oligonucleotide with sequence complementary to the HCMV immediate–early 2 mRNA that interferes with HCMV replication at an early stage during the replication cycle (Mulamba et al., 1998). Its only current indication is for the local treatment of HCMV retinitis in AIDS patients.

In addition to the treatment of established HCMV disease, antivirals have also been used to prevent such symptomatic episodes, especially in transplant recipients. The first strategy, defined as prophylaxis, consists of administering an antiviral to patients during the first 3 months or so after transplantation. The second strategy, referred to as “preemptive therapy,” consists of using short courses of antivirals only for high-risk patients based on evidence of active viral replication (e.g., detection