Antiviral Treatment of Epstein-Barr Virus-Associated Lymphoproliferations

Stephan H. Oertel and Hanno Riess

Hämatologie und Onkologie, Humboldt-Universität Berlin, Charité Campus Virchow-Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany

Abstract

Epstein–Barr virus (EBV)-associated lymphoproliferations may arise in individuals with hereditary or acquired immunodeficiencies. T-cell dysfunction and resulting insufficient control of EBV infection is common to all these patients in whom EBV-associated lymphoproliferations develop. EBV is an oncogenic virus which induces proliferation and transformation of B-lymphocytes. Antiviral treatment may represent a causal treatment option with relatively low toxicity. Among the different antiviral drugs aciclovir and ganciclovir are not the drugs of choice, because in EBV-associated lymphoproliferations the viral thymidine kinase enzyme is not encoded regularly. The agent arginine butyrate has the ability to selectively activate EBV thymidine kinase genes in EBV-infected lymphoma cells. In combination with ganciclovir it has demonstrated efficacy in patients with EBV-associated lymphoproliferations after solid organ transplantation. The action of foscarnet, another antiviral agent, is directed against the viral DNA, independent of the presence of the viral thymidine kinase. In our experience treatment with foscarnet resulted in continuous complete remissions in patients with EBV-associated lymphoproliferations. These clinical experiences demonstrate the efficacy of antiviral treatment in EBV-associated lymphoproliferations.

Introduction

Epstein-Barr virus (EBV) is a lymphotropic virus of the herpes virus family. Other members of this family are herpes simplex virus (HSV), varicella zoster virus (VZV) and human herpes virus 8 (HHV8). EBV

Recent Results in Cancer Research, Vol. 159
© Springer-Verlag Berlin Heidelberg 2002
persists latently in B-lymphocytes after the primary infection, which occurs in more than 90% of humans in childhood or adolescence. The acute, lytic primary infection normally occurs between the ages of 2 and 5 years and is clinically inapparent in most children. Apparent acute symptomatic EBV infection causes infectious mononucleosis [1]. EBV expresses approximately 11 proteins in its latent state; these maintain the episomal state of the virus in B-lymphocytes. EBV cytotoxic T-cells are responsible for the control of these EBV-infected B-lymphocytes and can be detected lifelong in healthy patients after infection. The proliferative and transformational abilities of EBV can be demonstrated experimentally in vitro. The EBV genome can be detected in various malignant diseases; Hodgkin's disease, nasopharyngeal carcinoma and Burkitt lymphoma are examples in immunocompetent patients [2, 3].

Patients with primary and secondary immunodeficiencies such as Wiskott-Aldrich syndrome, combined severe immunodeficiency or human immunodeficiency virus infection, and patients immunosuppressed due to drugs such as organ transplant recipients and those with connective tissue disease, have a high risk of developing EBV-associated lymphoproliferations. The development of EBV-associated lymphoproliferations in immunodeficient humans is triggered by the EBV, its proteins and an impaired immunoresponse to EBV. The histological appearance and clinical course can differ dramatically from those of lymphomas in immunocompetent patients. The improvement of immunosurveillance, if this is possible, can result in the complete disappearance of lymphomas [4].

Antiviral Treatment of EBV-Induced Lymphoproliferations

If these EBV-induced lymphoproliferations are considered to be the consequence of insufficiently controlled viral replication, antiviral treatment may be a causal treatment approach.

Aciclovir was the first antiviral drug with a specific activity against herpes viruses. Valaciclovir is a prodrug of aciclovir with a better oral availability and famciclovir is a prodrug of penciclovir; both have a spectrum against viruses very similar to aciclovir. Another important antiviral drug is ganciclovir. This drug dramatically improved the therapeutic options for herpes virus infections especially in cytomegalovirus (CMV) disease and preemptive treatment of CMV disease. Foscarnet and cidovovir are two further drugs with a high activity against herpes viruses.

Like HSV and VZV, EBV encodes a thymidine kinase enzyme. In a rate-limiting step, the viral thymidine kinase enzyme converts syn-