Case report

Adefovir added to lamivudine for hepatitis B recurrent infection in refractory B-cell chronic lymphocytic leukemia on prolonged therapy with Campath-1H

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Abstract

We describe a case of severe reactivation of occult hepatitis B virus infection in a 49-year-old man, who was treated with high doses of chlorambucil for a Binet stage A B-cell chronic lymphocytic leukemia (B-CLL). The patient was initially treated with lamivudine and subsequently with lamivudine and adefovir dipivoxil combination therapy to control viral replication and allow for long-term anti-cancer chemotherapy with alemtuzumab (Campath-1H), which was introduced to rescue for a B-CLL relapse. During 20 months of anti-HBV therapy, ALT and HBV-DNA levels progressively declined and B-CLL was successfully kept under control by long-term alemtuzumab administration.

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1. Case history

In 1989, a 49-year-old man who tested negative for hepatitis B surface antigen (HBsAg) and antibodies to HBsAg but positive for antibodies to hepatitis B core antigen (anti-HBc, AXSYM, Abbott Laboratories, North Chicago, IL, USA), was diagnosed as having Binet stage A B-cell chronic lymphocytic leukemia (B-CLL). One year later, the patient developed hepatosplenomegaly and progressive leukocytosis requiring cytotoxic treatment with low-dose chlorambucil (ld-Chl—5 mg/day), that led to partial remission of the hematological disease after 4 months of therapy (Cheson et al., 1996). The disease was maintained under clinical control, during the following 12 years, by repeated cycles of the same therapy, for a total dose of chlorambucil of 3500 mg.

In May 2002, because of a B-CLL relapse, the patient was given high-dose chlorambucil (HD-Chl 0.5 mg/kg/day; 35 mg/day for 5 days monthly) for a total of six cycles which led to partial remission of the disease. At this time point, the patient tested positive for serum anti-HBc alone.

Two weeks after the end of alkylating therapy (December 2002), liver function tests raised to abnormal values (AST = 288 IU, ALT = 344 IU, GGTP = 435 IU, bilirubin = 1.1 mg/dl) whereas HBsAg, hepatitis B e antigen (HBeAg), IgM anti-HBc and HBV-DNA (8 log10 copies/mL; Bayer Versant HBV DNA 3.0; sensitivity limit of 3.3 log10 copies/mL) became detectable in the serum. The patient neither had risk behaviours for HBV nor did he receive blood transfusions in the previous 6 months. Ultrasound examination of the abdomen was otherwise unremarkable, apart from slight hepatosplenomegaly. In April 2003, HBsAg and HBV-DNA were still detectable in serum; the patient underwent a liver biopsy that showed discrete infiltration by leukemic cells in the context of mild chronic hepatitis B, as revealed by hepatocytes staining for HBCAg...
and HBsAg. To prevent chemotherapy-induced flares of hepatitis B, lamivudine therapy was started at daily doses of 200 mg. During the first four months of lamivudine, ALT fell to normal values and the serum viral load fell to 5.2 log_{10} copies/mL.

In November 2003, a further leukemic B-CLL relapse occurred, despite extensive treatment with alkylating agents. Low doses (10 mg three times a week) of monoclonal antibody alemtuzumab (Campath-1H) were started, accordingly. In February 2004, following a rise in serum ALT and HBV-DNA levels and the need of potentiating cytostatic treatment to 30 mg, 10 mg/day adefovir dipivoxil was added to ongoing lamivudine. Lamivudine-resistant strains harbouring the M204I mutation, were identified by INNO-LiPA assay (HBV, Innogenetics NV, Belgium) in a serum sample collected prior to adefovir administration. During 10 months of combined lamivudine and adefovir dipivoxil treatment, ALT levels persistently fell within the normal range and serum HBV-DNA progressively declined to 4.7 log_{10} copies/mL (see Fig. 1). In the last available serum sample, the ADV-related mutations rtN236T and rtA181V, were not detected. During adefovir dipivoxil treatment renal function was unaffected and the patient did not experience any adverse reaction while remained in excellent clinical conditions.

2. Discussion

Reactivation of hepatitis B is a well-documented complication of tumor chemotherapy and immunosuppressive treatments, being observed both in patients with overt hepatitis B (HBsAg seropositive) as well as in those with occult infection (HBsAg seronegative) (Dhedin et al., 1998; Ma et al., 2003; Marusawa et al., 2001; Seth et al., 2002). Occult HBV infection is likely to be more common than previously recognized and to bear important clinical consequences (Raimondo et al., 2005). Reactivation of occult hepatitis B has been long recognized as a potential risk for patients with haematological malignancies undergoing anticancer chemotherapy. The availability of powerful antiviral treatments against HBV, allows now for prevention and management of this HBV related complications. Current guidelines for patients undergoing anti cancer chemotheraphy suggest pre-emptive therapy with lamivudine to prevent HBV recrudescence for HBsAg seropositive patients, only. For patients with occult infection, pre-emptive therapy is suggested in the set of organ transplantation related immunosuppression, only (Ahmed and Keeffe, 1999; EASL Jury, 2003; Lau et al., 2003; Rossi, 2003; Rossi et al., 2001).

We report here the first case in whom combination of lamivudine and adefovir dipivoxil allowed a safe and long-term Campath-1H treatment in a lamivudine resistant patient with advanced B-CLL. Previously, three HBsAg seropositive patients with B-CLL on Campath treatment who required lamivudine therapy as secondary prophylaxis for HBV reactivation, were reported (Heider et al., 2004; Inuito et al., 2005). Campath-1H is a monoclonal antibody directed against the CD52 antigen. It targets normal and malignant B and T lymphocytes through different cytotoxic mechanisms (i.e. complement cascade, antibody-dependent cell-mediated cytotoxicity, and apoptosis) and therefore exerts a profound and durable immunosuppression, in particular T-cell depletion and deficiencies in the cell-mediated immunity (Lundin et al., 2004).

To date, lamivudine is recommended for the treatment of acute HBV infections in the immunocompromised patients (Clark et al., 1998; Perrillo et al., 1999; Rossi, 2003). In patients with chronic hepatitis B, the long-term efficacy of this lamivudine is eroded by development of lamivudine-resistant, which predisposes to hepatitis flares and acute liver failure (Di Marco et al., 2004; Mutimer et al., 2000). We elected to continue lamivudine therapy in our patient who developed lamivudine-resistance since previous reports showed an increased risk of wild-type HBV related recrudescence of hepatitis B following interruption of lamivudine administration (Peters et al., 2004). The nucleotide analogue adefovir dipivoxil was added because it profoundly and persistently inhibits lamivudine-resistant HBV strains while co-presence of lamivudine reduces the risk of emergence of adefovir dipivoxil mutants (Benthamou and Poynard, 2003; Perrillo et al., 2004; Peters et al., 2004). Combination anti-HBV therapy with lamivudine and adefovir dipivoxil persistently suppressed serum HBV-DNA

Fig. 1. Serologic profile of patient with hepatitis B virus reactivation treated with lamivudine and adefovir dipivoxil on prolonged therapy with Campath-1H. Month 0 represents the 2 weeks after the end of high-dose chlorambucil (HD-Chl) treatment.
along with the risk of hepatic flares, thus allowing Campath treatment to be brought for 10 months.

Our findings indicate therefore that treatment with lamivudine and adefovir dipivoxil could be indicated for patients with hepatitis B reactivation associated with lamivudine-resistance during anti-cancer therapy.

References


