Bone Marrow Transplantation, (1998) 21, 1267–1269

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Case report

Lamivudine treatment for chronic replicative hepatitis B virus infection after allogeneic bone marrow transplantation

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Summary:

The risk of severe hepatic damage in patients with chronic hepatitis B virus (HBV) infection is well known; more effective treatments for this infection are needed. Lamivudine is being studied in immunocompetent and immunosuppressed HBV infected patients. We report a patient suffering from chronic replicative HBV infection after allogeneic BMT, who responded to lamivudine therapy. A 24-year-old woman with CML received an allogeneic BMT from her HLA-identical sister in June 1992. Before transplant, her HBV status demonstrated viral contact without active infection (HBsAb+, HBcAb+ IgG, HBeAb+). Four months after BMT mild chronic liver GVHD appeared, requiring immunosuppressive treatment. Antibodies to HBV completely disappeared post-transplant. Acute icteric hepatitis occurred 2 years later, with HBsAg+, high level of HBV-DNA, HBeAg+ and HBcAb IgM+. Lamivudine 100 mg/day rapidly reduced transaminase levels and effected HBV-DNA disappearance within 2 months. The treatment was well tolerated; no hematological side-effects occurred. This preliminary observation warrants further investigation of lamivudine treatment in bone marrow transplanted patients with active HBV infection.

Keywords: lamivudine; chronic hepatitis B virus infection; bone marrow transplantation

Hepatitis B virus (HBV) infection is a serious epidemiological and clinical problem in patients undergoing BMT. The infection can progress to chronic liver disease, cirrhosis and hepatocarcinoma; moreover, the reactivation of latent HBV infection, which may lead to fulminant hepatitis, has been reported at immune reconstitution after BMT.[1] In European BMT candidates the median prevalence of HBV infection is 3.5% (range 0–15%).[2,3] The use of positive hepatitis B surface antigen (HBsAg+) donors increases the risk of severe liver disease in BMT recipients.[1] Only a few drugs may be effective for treating active HBV infection, including α-IFN, famciclovir and lamivudine. We report the use of lamivudine for the treatment of chronic replicative HBV infection in a patient who had undergone allogeneic BMT for CML.

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Received 20 October 1997; accepted 15 January 1998

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Ph-positive CML in chronic phase was diagnosed in a 24-year-old woman in October 1990. At that time she had antibodies against hepatitis B surface antigen (HBsAb), core antigen (HBcAb, IgG), and e antigen (HBeAb). Pretransplant treatment included hydroxyurea and α-IFN. In June 1992 she underwent allogeneic BMT from her HBsAg negative HLA-identical sister, after conditioning with busulfan and cyclophosphamide. GVHD prophylaxis was CsA and short-course MTX. Engraftment was documented on day 25, when the neutrophil count reached 500/μl. Four months later the patient showed increased transaminases, bilirubin, alkaline phosphatase and γ-glutamil-transferase; her serum CsA level was in the therapeutic range (900 ng/ml by Abbott Laboratories polyclonal assay (Abbott Laboratories, Chicago, IL, USA)). A liver biopsy documented hepatic GVHD; immunohistochemistry showed absence of HBsAg and HBcAg in hepatocytes. Immunosuppression was potentiated by the addition of methylprednisolone (60 mg/day), and serum hepatic enzymes and bilirubin decreased. After 6 months, CsA was withdrawn and the patient was maintained with methylprednisolone and azathioprine, owing to a moderate chronic hepatic GVHD. Nine months after BMT, HBsAb and HBeAb disappeared from the serum; after a further 8 months, HBcAb was also undetectable. Three years after BMT the patient had an episode of acute icteric hepatitis due to HBV infection: HBsAg, HBcAb IgM and HBeAg became detectable in the serum. The disease remained active for more than 1 year, with altered serum transaminase ($5 \times$ NV); a high level of serum HBV-DNA (2400 pg/ml, Abbott Genostics TM liquid hybridization assay) was found in December 1996. Hepato-splenic ultrasound showed hepatomegaly with no signs of cirrhosis. The patient refused a repeat liver biopsy. In February 1997, treatment with lamivudine 100 mg/day orally was started. Serum transaminases remained unchanged ($5 \times$ NV) for a month, then showed a sudden increase to $20 \times$ NV which spontaneously subsided in 4 weeks, reaching values close

to normal 4 months after the start of treatment. No lamivudine side-effects were noticed during treatment. HBV-DNA completely disappeared from the serum 2 months after the start of treatment, concomitantly with the flare-up of transaminases, and remained undetectable at the subsequent controls. Five years after BMT, she is in continuous complete hematological and cytogenetic remission from CML; HBsAg is still present in the serum, while HBeAg has disappeared. A mild increment of transaminase, γ-glutamil transferase and alkaline phosphatase persists, probably due to the pre-existing chronic hepatic GVHD. The plan is to interrupt lamivudine and continue azathioprine treatment.

Discussion

The standard treatment of chronic replicative HBV infection (defined as HBeAg, HbcAb IgM and HBV-DNA positive) is high-dose α-IFN (a 16 week course with 10 MU, three times a week s.c.).[4] However, this treatment is effective in less than half of patients, and patients with very high serum levels of HBV-DNA rarely respond.[5] Side-effects at this dosage include myalgia, fever, leuko- and thrombocytopenia, neuropsychiatric disturbances and induction of auto-antibodies. Moreover, in allogeneic bone marrow transplanted patients high-dose α-IFN may facilitate GVHD development or may worsen pre-existing GVHD, due to enhancement of immunologic reactivity.[6]

Lamivudine is a new nucleoside analogue which can be administered orally, with strong activity against replicative HBV infection. It is an inhibitor of reverse transcriptase which is necessary to transcribe the HBV-RNA pregenome into HBV-DNA.[7,8] A preliminary study has shown that lamivudine treatment may induce complete and sustained suppression of HBV-DNA in patients with chronic replicative HBV infection.[8] In that study, most of the patients treated had not responded to α-IFN therapy and it was thought that the previous IFN treatment may have contributed to the subsequent success of lamivudine therapy. We decided not to use α-IFN in our patient, in view of the high serum HBV-DNA level and the risk of worsening the coexisting hepatic GVHD. Even in the absence of α-IFN treatment, after 4 months with lamivudine a marked reduction of transaminases and complete suppression of serum HBV-DNA were observed, in the absence of side-effects; later, even HBeAg disappeared. Increased transaminase levels after the start of lamivudine treatment have already been observed;[7,8] our patient showed an amplification of this phenomenon, with an acute hepatitis-like peak followed by a spontaneous regression. It is worth noting that at the dose used lamivudine did not show any hematological toxicity. It is interesting that our patient cleared her serum HBsAb, HBcAb and HBeAb after 9–17 months from allogeneic BMT, and remained negative during the early phase of hepatic GVHD (Figure 1). At that time, HBV infection was considered highly unlikely on the basis of liver histology, absence of viral particles on immunostaining and negativity of serological markers. The subsequent HBV infection behaved as a *de novo* infection (HBcAb IgM+). Although we cannot categorically exclude a reinfection, the patient had not received any blood products during the 2 preceding years; thus, the most likely explanation for the acute hepatitis was viral reactivation. This means that HBV may remain in the body as a latent infection even when HBsAb and HBcAb are present, and that HBV infection may reactivate even after the disappearance of the antibodies, as already suggested.[9]

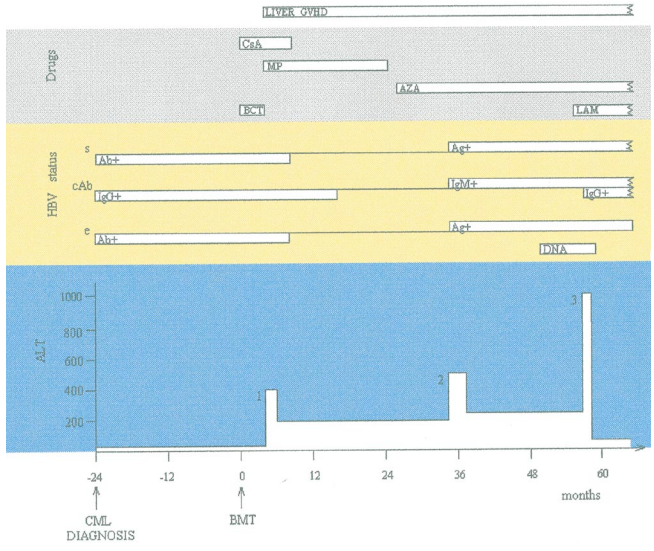

Figure 1 Hepatitis B virus marker and transaminase modifications in the reported patient. Transaminase peaks: 1, chronic hepatic GVHD; 2, HBV hepatitis; 3, lamivudine effect. BCT, blood component transfusion; MP, methylprednisolone; AZA, azathioprine; LAM, lamivudine.

Lamivudine as first line and single drug treatment proved to be effective and well tolerated in our patient. It is still uncertain how long the treatment should be maintained; a reasonable option is to stop the treatment on serum HBeAg disappearance, in order to avoid a possible rebound effect.[7,8] Finally, other studies are needed to explore the efficacy of this drug as prophylaxis in BMT patients who are HBsAg+ before transplant (analogous to liver transplant patients),[10] or who receive a bone marrow donation from an HBsAg+ donor.

Acknowledgements

We wish to thank the Glaxo Wellcome Research and Development (Greenford, Middlesex) for allowing compassionate use of lamivudine.

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