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Successful Long-Term Control With Lamivudine Against Reactivated Hepatitis B Infection Following Intensive Chemotherapy and Autologous Peripheral Blood Stem Cell Transplantation in Non-Hodgkin's Lymphoma: Experience of 2 Cases

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It is well documented that cytotoxic treatment in patients carrying the hepatitis B virus (HBV) enhances the risk of severe hepatic damage. Recently lamivudine has been reported to be effective in suppressing the replication of HBV under such conditions. Here we report two cases with HBV carrier status and with non-Hodgkin's lymphoma who were successfully treated with high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation with the administration of lamivudine to prevent HBV flare-up. The antiviral effect of lamivudine was fair, and no objective side effect was experienced during the transplant procedure. Both patients were followed carefully for more than a year without the appearance of the resistant virus. The rebound phenomenon in which HBV proliferates abruptly has not been experienced after withdrawal of lamivudine. We suggest that lamivudine is indicated both in the treatment of HBV viremia and in the prevention of proliferation of HBV in patients with HBV carrier status undergoing high-dose myeloablative chemotherapy. Am. J. Hematol. 70:60–63, 2002.

Key words: lamivudine; hepatitis B reactivation; myeloablative chemotherapy; lymphoma

INTRODUCTION

Reactivation of chronic hepatitis B in patients receiving cytotoxic chemotherapy for malignant diseases is well documented [1,2]. Recently lamivudine, a reverse transcriptase inhibitor, was reported to be effective in the management of hepatitis B virus (HBV) reactivation after intensive chemotherapy for malignant lymphoma [3,4]. But, there are only a few cases that report the effectiveness of the prophylactic usage of lamivudine in myeloablative high-dose chemotherapy with short follow-up period.

Here we report our experience of 2 cases with HBV carrier status who were treated successfully with high-dose chemotherapy rescued by autologous peripheral blood stem cell transplantation (APBSCT) under the administration of lamivudine with long-term follow-up.

CASE REPORT

Case 1

A 53-year-old male was admitted to a hospital because of progressive abdominal fullness in January 1998. He was noted as having an abdominal bulky mass, massive ascites, and pleural effusion and was diagnosed with non-Hodgkin's lymphoma of the diffuse large-cell type by cervical lymph node biopsy. Because initial chemotherapy with CHOP resulted in poor response, he was referred to our hospital for

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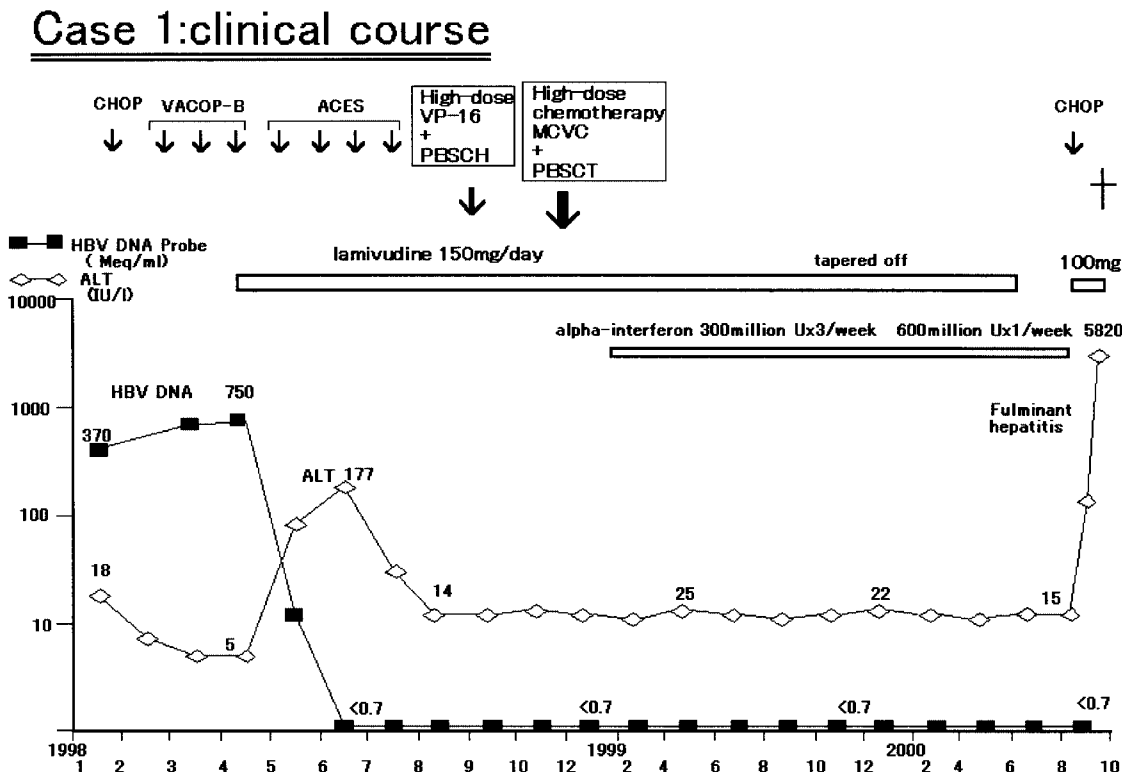

Fig. 1. Change in the serum levels of HBV DNA and alanine transaminase (ALT) with lamivudine treatment during the chemotherapy course of Case 1. Abbreviations: PBSCH, peripheral blood stem cell harvest; PBSCT, peripheral blood stem cell transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine, predonisolone; VACOP-B, VP-16, doxorubicin, cyclophosphamide, vincristine, predonisolone, bleomycin; ACES, ara-c, CBDCA, VP-16, methylpredonisolone. High-dose VP-16 consists of VP-16 (500 mg/m^2 × 3). High-dose chemotherapy (MCVC) consists of MCNU (200 mg/m^2 × 2), cyclophosphamide (50 mg/kg × 2), VP-16 (500 mg/m^2 × 3), and CBDCA (300 mg/m^2 × 4).

further chemotherapy in March 1998. Salvage chemotherapy was performed with the ACES protocol, which consisted of CBDCA (150 mg/m^2 × 2), VP-16 (40 mg/m^2 × 4), and high-dose Ara-C (2 g/m^2 × 1), and a good response was obtained.

He was known to be a chronic HBV carrier with HB surface antigen (HBsAg) positivity and HB e antigen (HBeAg) positivity. Although his transaminases were in the normal range, HB virus was detected in his blood at 370 Meq/mL by the DNA probe method upon admission to our hospital, and the virus increased to 670 Meq/mL at the end of March.

It was expected that serious hepatitis would complicate his clinical course and that the chemotherapy itself would be difficult to deliver. We decided to start lamivudine administration with a daily dose of 150 mg beginning in April 1998. Virological response was fair, and HBV almost disappeared from his blood within a month. Because he was classified in the high-risk group, as judged by the international prognostic index (IPI), we planned high-dose chemotherapy followed by APBSCT as the front line approach. After he was in complete remission, the peripheral blood stem cells were collected, and high-dose chemotherapy with MCNU (200 mg/m^2 × 2), CBDCA (300 mg/m^2 × 4), VP-16 (500 mg/m^2 × 3), and cyclophosphamide (50 mg/kg × 2) was carried out, followed by APBSCT. Engraftment was rapid, repeated HBV DNA testing was negative, and his transaminase levels were kept within the normal range throughout the course of the intensive chemotherapy.

He was discharged from our hospital in December 1998 in complete remission and was followed without therapy for his lymphoma.

Lamivudine was continued for the next 12 months and was gradually tapered off with the addition of interferon injections (300 × 10^6 U × 3/week); finally lamivudine was stopped completely by June 2000. His serological state converted to HBeAg negativity and HBe antibody positivity; see Figure 1 for charted serum levels.

In September 2000, malignant lymphoma relapsed as tumor formation at his tongue root. Although HBV DNA was not detected in the blood, lamivudine was restarted at that time to perform the systemic chemotherapy. Shortly after the chemotherapy, his course was complicated with fulminant hepatitis, and he was found dead on the 12th day after the chemo-

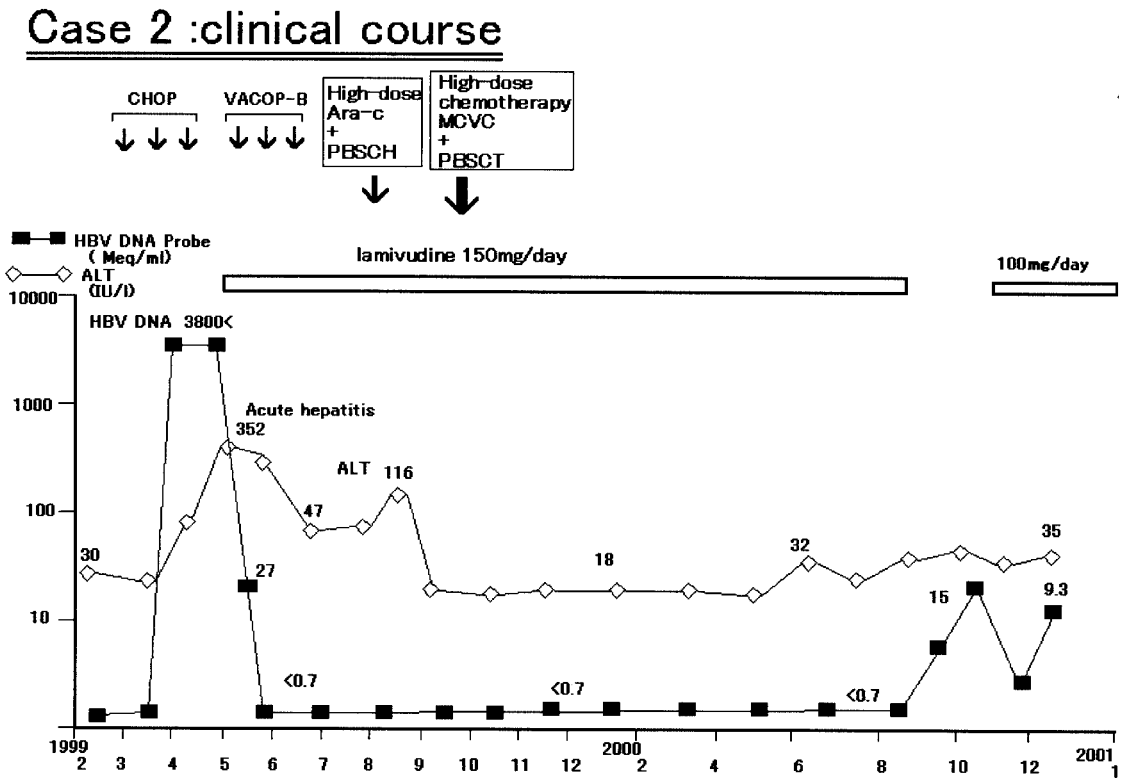

Fig. 2. Change in the serum levels of HBV DNA and alanine transaminase (ALT) with lamivudine treatment during the chemotherapy course of Case 2. See Figure 1 caption for abbreviations. High-dose Ara-c consists of ara-c (2 g/m^2 × 2/day × 2).

therapy. Liver necropsy revealed the histology of the fulminant hepatitis.

Case 2

A 43-year-old male was admitted to the hospital complained of general fatigue in January 1999. The abdominal CT scan revealed multiple space-occupying lesions (SOLs) in the liver. He was diagnosed as having non-Hodgkin's lymphoma of the diffuse large cell type by echo-guided needle biopsy. He was treated initially with CHOP chemotherapy, and, after 3 cycles, each of the SOLs in the liver regressed in size and partial response was obtained. But he also was known to be a HBV carrier with HBsAg positivity and HBeAg positivity from his youth. In April 1999, he began to complain of general fatigue and anorexia, and laboratory data revealed that the ALT was 352 IU/L and HBV DNA in his blood was more than 3,800 Meq/L. He was referred to our hospital, and we decided to start the administration of lamivudine at a daily dose of 150 mg to treat acute HB hepatitis. Two weeks later, the result of repeated examination of HBV DNA was reduced to 27 Meq/L, and also his symptoms were improved. The chemotherapy was restarted with a VACOP-B protocol without complication. Fine-needle biopsy of the residual SOL and the liver was performed in July 1999. It was revealed that the SOL was made up of necrotic tissue, and the liver tissue was graded as chronic active hepatitis. Because he was classified in the high-risk group as judged by the IPI at the initial presentation, we decided to treat with high-dose chemotherapy rescued by APBSCT as part of initial therapy.

After stem cells mobilized by chemotherapy and G-CSF were harvested, high-dose chemotherapy with MCNU (200 mg/m^2 × 2), VP-16 (500 mg/m^2 × 3), cyclophosphamide (50 mg/kg × 2), and CBDCA (300 mg/m^2 × 4) was administered followed by APBSCT in September 1999. Engraftment was rapid. The liver function tests remained normal, and HBV DNA was not detected in the blood throughout the course. After confirmation of continuous complete remission, he was discharged from our hospital in October 1999 and was followed without therapy for his lymphoma. Lamivudine administration was continued for the next 12 months and was then stopped (Fig. 2). After the lamivudine was stopped, the HBV DNA level in the blood started to increase gradually with slightly elevated transaminase levels, and lamivudine was restarted. His serological HBV state has remained unchanged.

DISCUSSION

Reactivation of HBV is a serious complication of the use of chemotherapy for treatment of malignant diseases in HBV carriers [1,2]. Especially following the profound immunosuppression of cytotoxic therapy in the treatment of malignant lymphoma, HBV is allowed to replicate and may provoke acute hepatitis and fulminant liver failure [5]. To prevent this complication, there have been only a few treatments, such as the choice of a steroid-free chemotherapeutic protocol [6] or α-interferon injections [7,8]. From our experience, the choice of steroid-free chemotherapy is generally unsatisfactory for prevention. As to α-interferon, retrospective analyses have shown that the response rate in chronic HBV infection is less than 50%, and the therapy is expensive and often not well tolerated [9]. Also α-interferon has myelosuppressive side effects and may influence the viability of hematopoietic stem cells. From our experience, α-interferon is usually unsatisfactory in treating activated HBV infection because of low response rate and many side effects.

Recently lamivudine, an oral nucleotide analogue that has a potent inhibitory effect on HBV reverse transcriptase, was introduced for clinical usage.

It is known to be effective in the treatment of acute and chronic active hepatitis and in the prevention of HBV reinfection in liver transplantation in the HBV carrier [10,11].

Also lamivudine demonstrates low cytotoxicity to a variety of bone marrow progenitor cells in vitro, and in HIV patients longer-term exposure is well tolerated with few side effects [12]. In the clinical situation where myeloablative chemotherapy is needed, such as for high-risk non-Hodgkin's lymphoma, lamivudine is appropriate because of its convenient administration and low cytotoxicity.

In this report we presented two patients with non-Hodkin's lymphoma and HBV carrier status who were treated successfully with administration of lamivudine. Although both of them were high-risk patients who needed myeloablative therapy, their HBV had begun to proliferate in the course of standard chemotherapy, and one of patient's course was complicated by acute hepatitis with icterus. After the start of lamivudine, HBV disappeared promptly from the peripheral blood, and the planned chemotherapy could be performed without delay. Peripheral blood stem cells could also be harvested successfully by the usual method, and high-dose chemotherapy could be carried out without problems.

There are few reports concerning the optimal period of lamivudine therapy after myeloablative therapy [3,4,13]. We carefully monitored the HBV DNA titer in the blood and followed the patients for more than a year until the withdrawal of lamivudine. We experienced neither HBV resistance to the drug nor the HBV rebound phenomenon in which HBV begins to proliferate abruptly after the withdrawal of lamivudine. Case 1 died from fulminant hepatitis without evidence of HBV proliferation. We speculate that it was drug-induced because HBV DNA was not detected in his blood and it took place shortly after the chemotherapy. In Case 2, HBV DNA began to be detected gradually after the withdrawal of lamivudine. Although his transaminases elevated only slightly without any clinical symptoms, lamivudine was started.

To our knowledge, there are only a few cases that report the effectiveness of the prophylactic usage of lamivudine in myeloablative high-dose chemotherapy. Thus, the two cases described here indicate the effectiveness and safety of lamivudine in preventing hepatitis B flare-up following high-dose chemotherapy.

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