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CASE REPORT

A prophylactic approach for bone marrow transplantation from a hepatitis B surface antigen-positive donor

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Abstract

It has been accepted that bone marrow transplantation (BMT) is the only curative therapeutic option for certain hematologic malignancies. The southeast Asia region is an endemic area of hepatitis B virus (HBV) infection; thus, BMT using a hepatitis B surface antigen (HBsAg)-positive donor is occasionally unavoidable. Organ transplantation using a HBsAg-positive donor can lead to post-transplantation de novo HBV infection and severe HBV-related hepatitis if no effective prophylactic measures are taken prior to and after transplantation. In this report, a four-level approach was designed for a patient with chronic myeloid leukemia, beginning with a booster HBV vaccination before performing BMT with a HBsAg-positive donor. Prior to BMT, the HBV viral load of the donor was reduced to an undetectable level by antiviral therapy. After BMT, hepatitis B immunoglobulin was administered intramuscularly for 1 wk together with a long-term antiviral drug, lamivudine. One year after discontinuation of lamivudine, the patient is still free of HBV infection.

Key words: Bone marrow transplantation; Hepatitis B virus; Vaccination; Hepatitis B immunoglobulin; Lamivudine.

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INTRODUCTION

Certain hematologic malignancies can only be cured by bone marrow transplantation (BMT). In the southeast Asian region, hepatitis B virus (HBV) infection is highly prevalent. BMT from donors exhibiting the hepatitis B surface antigen (HBsAg) is therefore occasionally unavoidable. Intensive chemotherapeutic drugs used in a conditioning regimen and post-transplantion immunosuppressive drugs are required to suppress host immunity and to prevent graft versus host disease (GVHD). Using grafts with HBsAg-positive hematopoietic stem cells is associated with severe liver injury and a high mortality rate[1-3]. In this report, we present a long-term follow-up study of a seronegative patient who underwent BMT with a HBsAg-positive donor in which a four-level approach for the prevention of HBV infection was utilized.

CASE REPORT

A thirty-seven year old man, a known case of chronic myeloid leukemia with positive Philadelphia chromosome in chronic phase, was previously treated with hydroxyurea. The patient planned to receive BMT from his sole HLA-identical sibling, his sister, who had been a known hepatitis B carrier. She was anti-HBe positive and had an HBV viral load of 5260 copies/mL, as indicated by the Amplicor HBV Monitor Test (Roche Diagnostics, NJ, USA). Lamivudine (100 mg/d) was initiated to suppress HBV DNA; and 3 mo later, her HBV viral load became undetectable. His antibody to HBsAg (anti-HBs) was firstly positive at a level of 10.3 mIU/mL. A booster dose of hepatitis B vaccine was given to him, and the subsequent anti-HBs level rose to 83 mIU/mL. A conditioning regimen for BMT containing busulfan (16 mg/kg) and cyclophosphamide (120 mg/kg) was started before the initiation of BMT. GVHD was prevented using methotrexate and tacrolimus. Lamivudine (100 mg/d) was initiated 7 d prior to BMT and was continued thereafter. From the day of BMT to the 7th d post-BMT, hepatitis B immunoglobulin (HBIg) 800 IU was injected intramuscularly daily in order to maintain the anti-HBs level > 1000 IU/L. From the 7th d post-BMT, the anti-HBs level was persistently over 1000 IU/L without HBIG administration. One month after BMT, while on tacrolimus for GVHD suppression and lamivudine for HBV prophylaxis, the patient's blood test results were as follows: HBsAg negative, anti-HBs positive (at 400 mIU/mL), anti-HBc positive, HBV viral load < 200 copies per ml and HBV PCR positive. HBV PCR became negative by 6 mo after BMT. The patient had only grade I acute GVHD and limited chronic GVHD. Tacrolimus was gradually tapered

off and then discontinued at the 15th mo post-BMT, and lamivudine was stopped 3 mo later. Two and a half years after BMT or 1 year after discontinuation of lamivudine, the patient felt well, and his blood tests indicated that he was HBsAg negative, anti-HBc positive, anti-HBs positive (at 14 mIU/mL) and HBV PCR negative.

DISCUSSION

The Asia-Pacific region is an endemic area of HBV infection, with a prevalence of more than 8%[4]. Most transplantation centers have regarded HBV infection as a relative contraindication for organ transplantation[5,6]. BMT with HBsAg-positive donors has been reported to be associated with an increased incidence of HBV-related hepatitis, severe liver-related complications, fatal liver failure and death[1,2,6-11]. However, a few reports show that HBsAg might be present transiently in some patients after receiving bone marrow graft from HBsAg-positive donors[1,2]. High HBV viral load in BMT donors and the absence of anti-HBs in BMT patients are two important risk factors predisposing a patient to the development of HBV-related hepatitis post-BMT[1,2]. Oral antiviral drugs are suitable to decrease the HBV viral load of the HBsAg-positive BMT donor. Lamivudine seems to be an appropriate antiviral drug in this situation because it causes rapid viral load reduction and because HBV resistance rarely occurs in a short period of lamivudine treatment[12]. Before BMT, the anti-HBs level in the present case report was increased to 83 mIU/mL by a booster dose of HBV vaccination. In general, the persistence of anti-HBV activity after BMT may be caused by residual recipient lymphocytes that have survived intensive conditioning regimens[3]. We decided to administer HBIg intramuscular injection from d 0 to d 8 post-BMT because the residual number of patient lymphocytes was uncertain. Anti-HBs level monitoring during the early post-BMT period showed that anti-HBs levels were over 1000 mIU/mL, resulting in the decision to discontinue HBIg 7 d post-BMT. HBIg was injected intramuscularly according to the protocol employed in HBV-related liver transplantation[13]. The mechanisms by which HBIg prevents graft re-infection are not completely understood. They may decrease the spread of HBV infection by neutralizing circulating viral particles and by inducing lyses of infected cells through pathways such as antibody-dependent cellular cytotoxicity[13]. Combination therapy of HBIg and lamivudine offers synergistic protection against HBV infection and appears to be more effective than a single agent for prophylaxis after HBV-related liver transplantation[13]. A recent study proposed a three-level approach when hematopoietic stem cell transplantation (HSCT) was performed with a HBV-positive donor[6]. The three-level approach consisted of a pre-HSCT reduction of HBV viral replication in donors by lamivudine, a pre-HSCT enhancement of the recipient's anti-HBV immunity by HBV vaccination, and finally, a post-HSCT suppression of HBV viral replication in recipients with lamivudine[6]. In that paper, patients received lamivudine for 52 wk after HSCT; however, our patient received lamivudine for 72 wk, and treatment with this drug was stopped 12 wk after the discontinuation of tacrolimus. A flare of HBV infection and severe hepatitis was reported if antiviral drug was withdrawn in patients with immunosuppressive status or upon completion of chemotherapy[14]. Continuing lamivudine for at least 3 mo after completion of chemotherapy or immunosuppressive drugs has been recommended by a recent practice guideline[15]. The HBV viral load, as determined by the Amplicor HBV monitor test used in this report, is far more sensitive than the Digene Hybrid Capture assay used in a previous report[6,16]. De novo HBV infection might appear in the long-term follow-up of antiviral-prophylactic BMT patients with HBV-positive donors whose viral load was determined to be negative using a low sensitivity assay. An additional benefit of post-transplantion HBIg may be anticipated in hematopoietic stem cell transplantation. Recently, HBIg and lamivudine treatment during BMT in a child who received BMT from her HBsAg-positive mother has been reported[17]. The child received lamivudine only 1 d before BMT and continued the drug for 102 d. The details of HBV viral load and HBV PCR, however, were not mentioned in that paper[17]. The authors suggested that HBIg and lamivudine combination may be useful during the early period of BMT[17]. Intramuscular injection of HBIg sometimes requires the correction of thrombocytopenia or changing the route of administration from intramuscular to intravenous injection. Due to the large dosage of intravenous HBIg and its high cost, it may not be affordable for all patients. Our strategies for using BMT from HBsAg-positive donors will require multicenter studies with a large number of patients and a longer follow-up before this costly, four-level prophylactic approach can be put into practice.

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