Prevalence, incidence and clinical outcome of hepatitis B virus and hepatitis C virus hepatitis in patients undergoing allogeneic hematopoietic stem cell transplantation between 2001 and 2004

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The prevalence, incidence and clinical course of viral hepatitis were prospectively determined in consecutive recipients of T-cell depleted hematopoieic stem cell transplants (49 mismatched, 60 matched, mean age 38 years; range 11-65). The prevalence of hepatitis B virus (HBV) was 15.6% and that of hepatitis C virus was 3.7% (HCV). HBV reactivated in one patient. Another developed *ex novo* acute hepatitis B which progressed to chronic hepatitis. There were no new cases of hepatitis C or worsening of pre-transplant HCV infections. HBV and HBC did not affect the outcome of T-cell depleted hematopoieic stem cell transplantation. Surveillance is important given the risk of HCV and HBV infection and/or reactivation and the efficacy of the new anti-hepatitis drugs.

Key words: HBV, HCV, HSTC, T-cell depletion, HLA disparity.

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Hepatitic diseases are one of the major complications after allogeneic hematopoietic stem cell transplantation (HSCT), with a mortality of 4% to 15%.[1] The mean prevalence of hepatitis B virus (HBV) infection in HSCT recipients is reported to be 1% in the USA and 3.5% in Europe.[2] The risk of fatal post-transplant HBV liver disease in patients who are persistently HBsAg positive is approximately 12%.[3] The prevalence of hepatitis C virus (HCV) antibody positivity in patients with hematologic malignancies varies widely from 47.5% in the pre-screening era[4] to the current 6%.[5]

Although HBV and HCV are both transmitted parenterally,[6] HBV is more closely associated with severe hepatitis and death and the patient's immunity strongly affects outcome.[7,8] Host-virus interactions underlie clinical manifestations of hepatitis B and C and liver cell damage appears to be caused primarily by host cell-mediated immune response. As documented by increased HBV-DNA serum levels, and widespread infection of hepatocytes, viral replication is markedly enhanced in severely immunosuppressed hosts, such as HSCT recipients.

Withdrawal of cytotoxic or immunosuppressive drugs gradually restores immune function, and in some patients results in rapid, massive hepatocyte necrosis , which causes severe hepatitis, hepatic failure and even death.[9,10] The diagnosis and monitoring of HBV and HCV infection in HSCT recipients has always been important. It is even more so today because lamivudine, adefovir and entecavir alone or in combination before starting chemotherapy effectively treat HBV infection and prevent reactivation when used pre-emptively.[11] Pegylated interferon combined with ribavirin,[12] which appears to be safe in HSCT recipients, is the best option for chronic HCV hepatitis, resulting in a 50% probability of cure.[13] This prospective study evaluated the prevalence, incidence and clinical course of HBV and HCV infections in patients who underwent T-cell-depleted allogeneic HSCT at the University of Perugia.

Design and Methods

All consecutive patients transplanted between January 2001 and December 2004 were evaluated. All patients received a strongly myeloablative conditioning regimen followed by the infusion of immunoselected peripheral blood CD34$^+$ cells. No post-transplant immunosuppressive treatment was administered as graft-versus-host disease prophylaxis.[14-16] Family members were assessed for HLA compatibility by standard methods. The case history and clinical, biochemical, and viral data were collected for each patient immediately before transplantation (baseline) and every 3 months post-transplant. Patients surviving at least 3 months after transplantation were eligible for analysis. HBV serology (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb) was screened in all recipients and donors using a micro-particle enzyme immunoassay (AxSYMSystem, Abbott Laboratories, Abbott Park, IL, USA). HBV-DNA detection was detected by polymerase chain reaction amplification using a commercial kit (HBV Monitor Roche, Roche Diagnostic Systems, Branchburg, NJ, USA), with a lower limit of detection of 1000 copies/mL. HCV serology was screened in each recipient and donor

using a third generation enzyme linked immunosorbent assay (ELISA, ORTHO Diagnostics System, Raritan, NJ, USA). HCV-RNA was detected using a commercial kit (Cobas amplicor HCV Monitor Roche, Roche Molecular System, Branchburg, USA), with lower limit of detection of 600 UI/mL.

Results and Discussion

A total of 109 patients (58 males, 51 females) were included in this study. Eleven patients came from northern Italy, 50 from the center (29 from Umbria), and 48 from the south and islands. The median age at transplantation was 38 years (range 11-65). Diagnoses were acute myeloid leukemia (n=59, 54%), acute lymphoblastic leukemia (n=24, 22%), multiple myeloma (n=9, 8%), chronic myeloid leukemia (n=8, 7%), Hodgkin's disease (n=4), non-Hodgkin's lymphoma (n=1), chronic lymphocytic leukemia (n=3) and myelodysplastic syndrome (5q-syndrome) (n=1). Conditioning consisted of total body irradiation (TBI), thiotepa, fludarabine and anti-thymocyte globulin (ATG) in 87 patients and thiotepa, fludarabine, ATG and melphalan in 22. Forty-nine patients received haploidentical transplants; 60 received HLA-identical transplants. The median follow-up after HSCT was 11.2 months (range 3-27).

HBV vaccination

Eleven of the 109 donors had been vaccinated against HBV, whereas 28/109 (25.7%) of transplant recipients had been vaccinated before the diagnosis of their hematologic malignancy. Twenty-four of these 28 showed an HBs-Ab titer > 10 mUI/mL and were considered responders.

HBV infection

Serology showed that 11 donors were anti-HBc and anti-HBs positive; one was only anti-HBc positive. Seventeen of the 109 transplant recipients (15.6%) showed positive hepatitis B serological markers at baseline. Fifteen patients had viral markers of previous infection (HBcAb and HBsAb). One patient had HBcAb alone with positive HBV-DNA at baseline (5.5 pg/mL). One 62-year old male showed active infection (HBsAg positivity). In February 2001, HBsAg positivity overlapped with the diagnosis of leukemia. This patient's baseline serology was: HBsAg-positive, anti-HBc-positive, anti-HBc-IgM-negative, HBeAg-negative, anti-HBe-positive, HBV-DNA negative. Liver tests were normal. Prophylaxis with nucleoside analogs was not given, in accordance with the Seattle Study Group's recommendations for HBV-DNA-negative recipients. The patient died of severe graft-versus-host disease on day 106 after transplantation. HBV-DNA was undetectable on day 90 post-transplant.

Reactivation of HBV occult infection

Occult HBV infection reactivated in 1/15 recipients (6%) with anti-HBc and anti-HBs positivity 15 months after transplantation. In this 49-year old man with acute leukemia HBsAg appeared, anti-HBs cleared and anti--HBc-IgM, HBeAg and HBV-DNA became positive; serum transaminase activity remained normal. The patient did not respond to lamivudine 100 mg/day; therapy with adefovir was discontinued after a very short time because the patient's pre-existing renal failure worsened. The patient is currently off-therapy with undetectable HBV-DNA and normal serum transaminase activity.

A new case of hepatitis B

A 33-year old man with acute myeloid leukemia, who was HBV negative at baseline, developed acute hepatitis B without jaundice 6 months post-transplant. Serology showed that he was HBsAg positive, antiHBc-IgM positive, HBeAg negative, and antiHBe positive. The source of infection remained unknown as all tests on donors of blood transfusions and the donor of the hematopoietic stem cell graft were negative. Hepatitis B progressed to become chronic and was treated with adefovir (10 mg/day). Biochemical and viral responses were good but the patient died 10 months later from relapsed leukemia.

HCV infection

All donors were anti-HCV negative. Four of the 109 patients (3.7%) were anti-HCV positive at transplantation. Only one of these four recipients was HCV-RNA positive (>10^5 copies/mL) with genotype 1b. Serum transaminase activity was normal in all four patients. No evidence of hepatitis was observed in these four patients at any time during the follow-up. No new case of HCV infection developed during the follow-up

HSCT recipients are at high risk of HBV and HCV infections because of repeated hospital stays, blood transfusions, invasive and instrumental procedures and profound immunosuppression. Furthermore, the risk of hepatitis reactivation, particularly of HBV infections[17] and reversion of anti-HBc and anti-HBs positivity,[18,19] has recently been well-established. Since this study was started in 2001 it has been now recommended that transplant recipients with current or past hepatitis infections are monitored more frequently than at the 3-month interval established in this protocol. This prospective study showed relatively high pre-transplant prevalences of HBV (15.6%) and HCV (3.7%) infection in T-cell depleted HSCT recipients from different Italian regions. A minority of patients (25.7%) had been vaccinated, and the response rate in these was similar to that occurring in the general population. Only 11/109 donors had been vaccinated against hepatitis. Serology in the transplant recipient with reactivation of hepatitis B was indicative of a previous infection. He had been transplanted from a donor who had not been vaccinated and whose serology was negative. In this series we observed one new case of acute hepatitis B which progressed to become chronic. One HBsAg positive patient, who was HBV-DNA negative at the time of transplantation and was not prophylactically treated with nucleoside analogs, did not show any later reactivation. No new cases of hepatitis C or worsening of previous HCV infections were observed and no patient has died of

liver failure. HBV and HCV did not significantly affect outcomes after T-cell-depleted HSCT, suggesting that extensive T-cell-depletion of the graft minimizes transplant-related toxicity and that the lack of pharmacological immune suppression post-transplant as prophylaxis against graft-versus-host disease may reduce the risk of HBV or HCV reactivation. However, definitive conclusions cannot be drawn from these results beyond recommendations to monitor all recipients of T-cell-depleted transplants closely until full immune reconstitution has been established. Close surveillance of anti-HBc and anti-HBs positive patients and early pre-emptive therapy with nucleoside analogs in those with HBV reactivation, and pegylated-interferon combined with ribavirin for patients with HCV contribute to preventing liver dysfunction and hepatitis-related deaths. Furthermore pre-transplant vaccination of HB-negative donors may be beneficial.[20]

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