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CASE REPORT

Liver transplantation for acute hepatic failure due to chemotherapy-induced HBV reactivation in lymphoma patients

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Abstract

Hepatitis B (HBV) reactivation induced by chemotherapy is problem encountered recently in the management of malignant diseases. Chemotherapy-induced HBV reactivation may ultimately lead to terminal acute liver failure. Liver transplantation (LT) currently remains the only definitive treatment option for such cases, but is generally denied to patients suffering from malignancy. Here, the authors describe 2 cases of cancer-free and HBV graft re-infection-free survival after LT performed for terminal liver failure arising from HBV reactivation induced by chemotherapy for advanced stage lymphoma. These 2 cases, and some other reports in the literature, may suggest that patients suffering from hematologic malignancies and terminal liver disease can be considered for LT if the prognosis of their hematologic malignancy is good.

Key words: Liver transplantation; Contraindication; cancer; Liver failure; Chemotherapy; Hepatitis B virus

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INTRODUCTION

Reactivation of a previous hepatitis B virus (HBV) infection is a known complication in patients undergoing chemotherapy or immunosuppressive treatment. Such reactivations have been observed in HB surface antigen (HBsAg) positive and negative subjects, with an incidence of 26% to 47%[1,2]. Although lamivudine prophylaxis is considered as the treatment of choice in such

situations, in some cases it may not prevent reactivation of the underlying infection[3]. Chemotherapy-induced HBV reactivation may then lead to terminal liver failure, with very limited treatment options, as life-saving liver transplantation (LT) is generally not performed in patients suffering from preexisting extrahepatic malignancies[4]. We report 2 cases of long-term cancer-free and HBV graft re-infection-free survival after LT for HBV reactivation induced by chemotherapy administered for advanced staged lymphoma.

CASE REPORTS

Case 1

A 49-year-old Caucasian male was diagnosed with advanced nodular sclerotic Hodgkin's lymphoma stage IIIb-IV in January 2006. In the following month, chemotherapy was initiated using 4 cycles of escalated BEACOPP regimen (bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine, prednisone). After 3 cycles, blood analyses indicated an acute HBV infection (HBsAg+, anti-HBc+). Indeed, prior to chemotherapy, the patient had been an HBsAg carrier, a status he had failed to mention initially. Further blood tests confirmed the revised diagnosis of chronic HBV infection (anti-HBs-, anti-HBe+). His hepatic function was closely monitored and the last cycle of escalated BEACOPP was administered in April 2006. A follow-up positron emission tomography (PET) revealed significant lymphoma regression, after which the patient was switched to a baseline BEACOPP pattern, to minimize adverse effects.

One month later, after the first cycle of baseline BEACOPP chemotherapy, the patient was admitted to hospital with fatigue, anorexia, generalized edema and jaundice. Blood analysis showed significant alteration of liver function (aspartate aminotransferase: 505 IU/L, alanine aminotransferase: 300 IU/L, lactate dehydrogenase: 579 IU/L, T-bilirubin 45.9 mg/L), and further chemotherapy had to be postponed. Polymerase chain reaction for HBV-DNA was performed with positive results (HBV-DNA > 10 000 000 copies). Lamivudine therapy was then initiated. In June 2006 the patient presented with liver failure (MELD (Model for End-stage Liver Disease) score 35, Quick < 20%, Factor V < 20%, international normalized ratio > 5) and hepatic encephalopathy. Additional serology performed for other pathogens remained negative (human immunodeficiency virus, HCV, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, toxoplasmosis), so that hepatic failure could only be attributed to the reactivation of the underlying HBV infection. He was then referred to our university hospital for LT evaluation, despite the fact that the last cycles of chemotherapy had not yet been administered. As the last PET showed no residual lymphoma activity, an emergency LT was performed. Immunosuppression was initialized using tacrolimus, mycophenolate mofetil and prednisone. Graft reinfection was prevented using anti-Hbs immunoglobulin injections and lamivudine. No further chemotherapy was administered. In the first 4 years of follow-up, regular computed tomography (CT) and PET scans did not show any evidence of lymphoma activity. Immunosuppressive treatment was gradually tapered as in other LT recipients. At 4-year follow-up, the patient was alive and well, cancer-free and HBV-free, on long-acting tacrolimus monotherapy and HBV prevention bi-therapy (lamivudine + anti-HBs immunoglobulin injections).

Case 2

A 53-year-old female originating from central Africa was diagnosed with big cell lymphoma type B of the stomach, with thoracic involvement in December 2006. Staged as IIIa, the patient underwent poly-chemotherapy using a R-ACVBP regimen (rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone). The last chemotherapy was administered in March 2007, and she was considered in full remission (negative PET, CT and gastroscopy). Despite her hepatitis B status (HBAg+, anti-HBc+, anti-HBs-, anti-HBe+) being known before chemotherapy initiation no preventive therapy was taken, and HBV reactivation was diagnosed in November 2007 (positive PCR). The patient immediately received lamivudine, which proved ineffective, resulting in terminal hepatic failure (MELD-score 29, Quick < 23%, Factor V < 30%) in March 2008. The patient was then referred for LT evaluation. An urgent LT has then been performed since stage 2 to 3 encephalopathy became apparent. Because of severe coagulopathy, hemostatis was difficult during the LT procedure, and splenectomy had to be performed at the same time. Pathology of the spleen did not reveal lymphoma. Graft HBV reinfection was prevented by anti-Hbs immunoglobulin injections and lamivudine, and initial immunosuppression consisted of tacrolimus, mycophenolate mofetil and prednisone, rapidly tapered. At 2-year follow-up, the patient was alive and well, and her immunosuppressive medication has been adjusted to long-acting tacrolimus monotherapy. She did not develop any sign of HBV or lymphoma recurrence.

DISCUSSION

This article reports 2 patients with lymphoma who underwent successful LT for chemotherapy-induced HBV reactivation. These cases demonstrate that life-saving LT should not be denied as an absolute contraindication in patients with lymphoma and chemotherapy-induced HBV reactivation. This concept confirms other reports suggesting that patients suffering from hematological diseases show low recurrence rates after LT[5,6]. These cases offer the opportunity to reconsider current LT limitations, particularly in those instances where transplantation would usually be denied. The authors consider that patients suffering from preexisting malignant diseases should not be excluded by default for this life-saving procedure, but that potential benefits and risks

must be evaluated individually particularly in malignant lesions affecting a younger and fitter population. This view was also recommended by the King's College Hospital group[7].

Reactivation of a previous HBV infection is an entity regularly encountered with chemotherapy. Cases of fatal fulminant or subacute HBV liver failure following chemotherapy for lymphoma have been reported[8-10]. This is particularly true in cases in which rituximab and corticosteroids are included in the protocol[1,2,8]. The pathophysiology remains to be determined, but reports suggest that immunosuppressants favor viral reproduction, and that a massive immunological reaction occurs as soon as normal immune system function is reestablished at the end of chemotherapy. This overwhelming immune response is the origin of hepatic acute cytolysis[1]. Reports suggest that every patient undergoing chemotherapy should be checked for previous HBV infection, and that HBV preventive treatment throughout the patient's chemotherapy should be performed in case of previous HBV infection. However, at the time of treatment of the 2 patients mentioned in this case report, lamivudine prophylaxis was not reimbursed by the Belgian health system so that it was administered only after reactivation had already occurred. Nonetheless in some cases, lamivudine prophylaxis may not prevent reactivation, and terminal or fulminant liver failure may occur[3]. Urgent LT is the only effective treatment[11,12] but is usually denied because of the underlying malignancy. To the best of the authors' knowledge, only a few cases of LT in this particular setting have been reported so far[5,8,13]. This suggests that patients suffering from hematologic diseases seem to constitute a subgroup in which the reoccurrence rate after LT seems to be low. These 2 cases do support these observations. To some extent these observations can be explained by the new treatment possibilities and the recent outcome improvements that have been made over the last few decades in the management of hematologic diseases. New chemotherapy regimens, as well as new methods (e.g. PET) to assess the efficiency of ongoing treatments, are being continuously developed, allowing tailored therapies for each patient, rendering this condition highly curable. Current studies suggest that an escalated BEACOPP regimen is the treatment of choice for advanced Hodgkin lymphoma, and has an overall chance of 96% to achieve full remission with a 5 year survival rate peaking at 92%[14-16]. Other complications such as veno-occlusive disease or graft-*versus*-host disease following bone marrow transplantation may also cause terminal liver failure in patients treated for hematologic malignancies. Though experience is limited, reports indicate that LT may also be a feasible and effective approach in such cases[17-19].

Recurrence of the underlying preexisting malignancy may occur after LT, promoted by the necessary immunosuppression and by a direct effect of calcineurin inhibitors[4,20]. However, in cancer patients with good prognosis, as in the 2 lymphoma patients described here, LT may be life-saving. In the absence of large studies, each patient should be assessed individually to evaluate if organ transplantation can be beneficial in terms of survival and quality of life. Further studies with longer follow-up are needed to establish prognostic factors to identify those patients in whom LT can be considered as an effective approach.

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