Lamivudine Prophylaxis for Chemotherapy Induced Reactivation Hepatitis B: A Case Report and Review

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Abstract

Reactivation hepatitis B as a result of chemotherapy induced immunosuppression is well documented in the medical literature. Complications range from anicteric hepatitis to fulminant hepatic failure and death. Although lamivudine has been successfully used to treat hepatitis B reactivation in cancer patients, its role as prophylaxis in these patients is less well defined.

We describe successful lamivudine prophylaxis of a patient with chronic hepatitis B undergoing chemotherapy for acute myelogenous leukemia (AML). We support the position that lamivudine may play a significant role in the successful prevention of reactivation hepatitis B in cancer patients undergoing chemotherapy.

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Introduction

Reactivation hepatitis B in cancer patients undergoing chemotherapy is well documented in the literature. In the setting of chemotherapy-induced immunosuppression, reactivation of hepatitis B can lead to a spectrum of adverse outcomes including fulminant hepatic failure and death. Lamivudine, a reverse transcriptase inhibitor, has been used to treat reactivation hepatitis in this subset of patients. Although prophylaxis is often suggested, reports are rare. We describe successful lamivudine prophylaxis of a patient with chronic hepatitis B undergoing chemotherapy for acute myelogenous leukemia (AML).

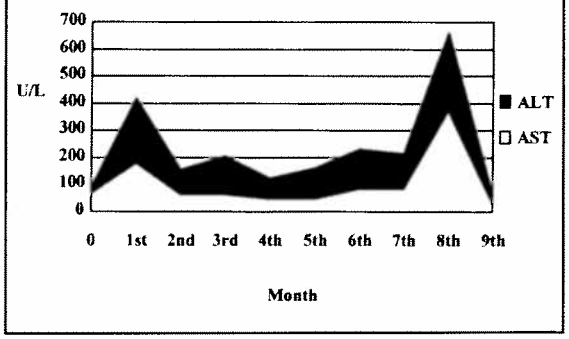
Case Report

The patient is a 25-year-old female with chronic hepatitis B who was diagnosed with AML after evaluation for buccal ecchymosis and extremity hematomas. Initial labs were remarkable for hepatitis B surface antigen (HBsAg) reactivity, hepatitis B virus (HBV) DNA of .03 pg/ml, aspartate aminotransferase (AST) of 69 U/L, and alanine aminotransferase (ALT) of 92 U/L.

She began prophylactic treatment with lamivudine prior to induction chemotherapy with idarubicin and cytarabine. Prophylaxis was continued throughout the subsequent consolidation chemotherapy, which included four cycles of high dose cytarabine. Aside from several episodes of neutropenic fever, she tolerated the chemotherapy well. Although the patient had persistently elevated liver associated enzymes (ALT ranging from 68 to 578 U/L and AST ranging from 27 to 180 U/L), HBV DNA levels remained undetectable and the patient had no clinically significant hepatic sequelae.

During her ninth month of treatment, the patient had a prolonged period of pancytopenia with bone marrow biopsy showing a relapse of her AML. After failed reinduction with mitoxantrone and etoposide, the patient was scheduled for an allogeneic bone marrow transplant. At that time, the patient's liver associated enzymes included an AST of 30 U/L and an ALT of 68 U/L. HBV DNA levels were still undetectable. The highest levels of transaminases occurred during induction and reinduction and were thought secondary to chemotherapy-induced hepatotoxicity (Figure 1).

Figure 1.— Transaminases during chemotherapy



Discussion

A spectrum of liver injury is associated with chemotherapy, ranging from anicteric hepatitis to fulminant hepatic failure and death. Etiologies include viral hepatitis, drug hepatotoxicity, malignant hepatic infiltration, shock, sepsis, and cryptogenic causes. A growing body of literature has concentrated on the adverse outcomes of chemotherapy patients with viral hepatitis.

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Reactivation hepatitis B in cancer patients receiving cytotoxic chemotherapy is well reported. Although most cases have involved hematological malignancies (ie. lymphoma), occasional cases involving solid tumors have been reported as well.[1] In a 1991 retrospective study of Chinese lymphoma patients, 27% were found to be HBsAg seropositive. Of these patients, 47% developed reactivation hepatitis during chemotherapy, which resulted in a 5% mortality.[2] In a similar Japanese study, 3.3% of lymphoma patients were found to have chronic HBV infection. Severe hepatitis occurred in 53% of these patients and mortality rates were as high as 24%.[3] In 2000, Yeo et al. conducted the first prospective assessment of HBV reactivation rates in Chinese cancer patients receiving cytotoxic chemotherapy. In this study, 12% of 626 consecutive cancer patients were HBsAg positive, and reactivation occurred in nearly 20% of these patients.[1] This data clearly supports the need for in depth assessment of this adverse process. Of note, hepatitis C infection has also been documented in association with chemotherapy-induced hepatitis, and mortality rates appear to be similar to that seen in patients with HBV reactivation.[4]

There are two proposed mechanisms of reactivation hepatitis B in cancer patients undergoing cytotoxic chemotherapy. The first involves immunosuppression, enhanced HBV replication, and direct hepatotoxicity from infection. The second mechanism involves a rebound immune response upon withdrawal of chemotherapy, resulting in hepatocyte destruction.[1]

Attempts to identify risk factors for reactivation hepatitis B have produced conflicting results. A 1990 study of 105 lymphoma patients by Liang et al. concluded that age, sex, stage, symptoms, lymphoma subtype, presence of hepatic lymphoma, treatment, presence of HBeAg and anti-HBe serologies, and underlying liver pathology were not predictive of hepatic complications.[5] However, a prospective study by Yeo et al. identified several significant associated factors. These included male sex, younger age, presence of lymphoma, chemotherapeutic agent (most common being corticosteroids, anthracyclines, cyclophosphamide, and vinca alkaloids), and HBeAg positivity (although some virulent precore mutant strains are unable to produce the eAg and are still highly associated with fulminant hepatic failure).[1]

Perhaps the most promising treatment for reactivation hepatitis in cancer patients is the use of lamivudine (3'-thiacytidine), a reverse transcriptase inhibitor. This nucleoside analog, originally used for HIV infection, was found to reduce HBV DNA to undetectable levels in 86% of HIV infected HBV carriers within two months.[4] Several successful pilot studies and four large multicenter randomized controlled trials showed that lamivudine therapy was associated with an increased rate of HBeAg seroconversion, improved serum ALT levels and liver histology, and a decrease in the development of cirrhosis.[6,7] In addition to its efficacy, lamivudine was associated with few if any side effects.[7] The drug was approved as therapy for HBeAg positive chronic hepatitis B patients in 1998. Lamivudine's role has subsequently been broadened to treat chemotherapy-induced reactivation hepatitis B. There are at least 13 documented case reports of successful lamivudine treatment of reactivation hepatitis, including those patients with fulminant disease.[4]

Lamivudine may also play an important role as prophylaxis for chronic HBV cancer patients prior to chemotherapy. By suppressing HBV DNA replication (as evidenced by histology and HBV DNA levels), lamivudine prevents hepatocyte infection, the rebound immune response, and subsequent reactivation hepatitis. Several case reports (including our own) and two recent studies, give direct support to this proposal.[8-12] In our patient, HBV DNA levels remained undetectable throughout chemotherapy, and transient elevations in her liver enzymes were secondary to chemotherapy-induced hepatotoxicity. In a retrospective Israeli study, 13 HBV infected cancer patients were prophylactically treated with lamivudine prior to and following immunosuppressive therapy, with a mean follow-up of 21 months. None of the patients had clinical or serological evidence of HBV reactivation during or after prophylaxis. Likewise, in a prospective Italian study, 20 consecutive patients with HBV and hematologic malignancies were prophylactically treated with 100 mg of lamivudine from the start of chemotherapy until one month after the end of treatment. Only one patient developed reactivation hepatitis during a median follow-up of six months.

Several unresolved issues regarding lamivudine prophylaxis need to be addressed. Specifically, optimal dose, duration of therapy, and resistance have been investigated in chronic HBV patients, but not in those patients undergoing chemotherapy. In a one year trial of lamivudine, Lai et al. showed that 100 mg daily was more effective than 25 mg in the extent of histologic improvement, degree of HBV DNA suppression, and prevention of fibrosis.[7] Duration of therapy and resistance have also been studied extensively, as prolonged lamivudine therapy allows for genotypic mutations in the YMDD locus of HBV that confers a reduced sensitivity to lamivudine. Resistance rates at one, two, three, and four years are 17%, 40%, 55%, and 67%, respectively. These patients typically have higher ALT and HBV DNA levels than those without resistance, but levels on average are still lower in affected individuals than their pretreatment values.[13-15] Continued histologic improvement is also seen with extended therapy regardless of YMDD resistance, as evidenced by liver biopsies from patients treated with two or more years of lamivudine in the Asian Multicenter trial.[16] In addition, a large co-

hort study showed no increased incidence of hepatic insufficiency or change in adverse events noted with the YMDD mutant HBV.[17] Therefore, while prophylaxis with 100mg of lamivudine for extended periods of time seems safe and effective in chronic HBV patients despite YMDD resistance, randomized double-blinded trials will be needed to better assess these issues in cancer patients undergoing cytotoxic chemotherapy.

Conclusion

There are 400 million cases of hepatitis B worldwide with prevalence rates in chemotherapy patients reported at 12%. Reactivation hepatitis occurs in 20-50% of these patients and is a potentially lethal complication, with mortality rates documented as high as 25% in affected individuals. Lamivudine therapy, originally used in HIV patients and then approved for HBeAg chronic HBV, has now been used to successfully treat reactivation hepatitis B in chemotherapy patients. We support the position that lamivudine should also be used as prophylaxis to prevent reactivation hepatitis in cancer patients, and we provide a case report of successful lamivudine prophylaxis.

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