Fatal hepatic decompensation in a bone marrow transplant recipient with HBV-related cirrhosis following lamivudine withdrawal

Annarosa FLOREANI (1), Sara BONINSEGNA (1), Salvatore LOBELLO (2), Diego CAROLI (1), Stefano FAGIUOLI (1)

(1) Department of Surgical and Gastroenterological Sciences, University of Padova; (2) S. Antonio Hospital, ASL 16, Padova, Italy.

SUMMARY

Lamivudine is a nucleoside analogue with a potent antiviral activity used as prophylaxis against hepatitis B virus reactivation in patients with chronic HBV infection receiving chemotherapy. No standard guidelines exist, however, for the duration of lamivudine treatment. We report a clinical case of a 56-year-old patient with HBeAg-negative cirrhosis who developed a multiple myeloma. He was treated with lamivudine for 1 year while receiving chemotherapy and a subsequent bone marrow transplant. Complete remission from multiple myeloma was achieved. Four months after lamivudine was withdrawn, he experienced HBV reactivation with jaundice, though no YMDD mutations were detected. The patient rapidly developed fatal decompensation with septicemia and renal failure. In conclusion, this case shows that physicians should avoid discontinuing nucleoside therapy in patients with HBV infection who undergo immunosuppression for concomitant neoplastic conditions.

Introduction

Hepatitis B virus (HBV) reactivation is a well-described complication of immunosuppression in cancer patients treated by chemotherapy and may result in varying degrees of liver damage [1]. The risk factors identified include male sex, younger age, HBeAg positivity, and a diagnosis of lymphoma [1, 2]. A Consensus Conference indicated that lamivudine is an effective drug for protecting against HBV reactivation during immunosuppression following chemotherapy [3]. Prophylactic lamivudine appears to prevent HBV reactivation and is associated with a significantly lower mortality rate than in patients not treated with lamivudine prophylaxis [4]. A number of articles have shown the benefits of lamivudine prophylaxis during chemotherapy for both solid malignancies and myeloproliferative disorders [5-12], but there are no standard guidelines on the best duration of lamivudine treatment. Some authors have suggested continuing for 4-6 months after completing antineoplastic treatment or undergoing transplantation [13, 14], but there is a risk that lamivudine withdrawal will induce serious flares of hepatic inflammation [15-17]. We report a clinical case of bone marrow transplant recipient with HBeAg-negative cirrhosis, who suffered fatal reactivation of HBV infection after lamivudine withdrawal.

Report

A 56-year-old Caucasian male with HBV-related cirrhosis was admitted to hospital in July 2004 with high serum transaminases and jaundice. He had been attending a liver outpatient clinic regularly since 1981, when he was found to be HBeAg-negative, anti-HBe positive, HBV-DNA negative, with normal transaminases. His liver function tests remained almost stable until 1997, when he experienced a “hepatitis flare” with raised transaminases. At that time, he was HBeAg-negative, anti-HBe positive, HBV-DNA negative, with normal transaminases. His liver function tests remained almost stable until 1997, when he experienced a “hepatitis flare” with serum transaminases above 10 times the normal limits, and positive HBV-DNA by Polymerase Chain Reaction (PCR). Hepatitis C, hepatitis delta, and human immunodeficiency virus infections have been ruled out. A liver biopsy was performed in June 1997, revealing a score 10 for grading, and a score 6 for staging, according to the Ishak modified histology activity index. Immunohistochemistry demonstrated HbcAg positivity in rare nuclei. No standard interferon treatment was given because of the poor response of the liver flare. Both his mother and two siblings are carriers of hepatitis B virus, but he does not have any other risk factors for HBV infection. He had been treated for a lymphoma in February 2002 and a systemic leukemia in January 2003, both of which responded to chemotherapy. A liver biopsy performed in September 2004 revealed a score 10 for grading and a score 6 for staging, according to the Ishak modified histology activity index. Immunohistochemistry demonstrated HbcAg positivity in rare nuclei. No standard interferon treatment was given because of the poor response of the liver flare. Both his mother and two siblings are carriers of hepatitis B virus, but he does not have any other risk factors for HBV infection.

In January 2003, the patient was diagnosed with multiple myeloma. In March 2004, he was referred to a hematologist because of a persistently raised serum transaminase level and a liver biopsy was performed. The patient was found to have a score 10 for grading and a score 6 for staging, according to the Ishak modified histology activity index. Immunohistochemistry demonstrated HbcAg positivity in rare nuclei. No standard interferon treatment was given because of the poor response of the liver flare. Both his mother and two siblings are carriers of hepatitis B virus, but he does not have any other risk factors for HBV infection. A liver biopsy performed in September 2004 revealed a score 10 for grading and a score 6 for staging, according to the Ishak modified histology activity index. Immunohistochemistry demonstrated HbcAg positivity in rare nuclei. No standard interferon treatment was given because of the poor response of the liver flare. Both his mother and two siblings are carriers of hepatitis B virus, but he does not have any other risk factors for HBV infection.

In January 2003, the patient was diagnosed with multiple myeloma. He was referred to a hematologist because of a persistently raised serum transaminase level and a liver biopsy was performed. The patient was found to have a score 10 for grading and a score 6 for staging, according to the Ishak modified histology activity index. Immunohistochemistry demonstrated HbcAg positivity in rare nuclei. No standard interferon treatment was given because of the poor response of the liver flare. Both his mother and two siblings are carriers of hepatitis B virus, but he does not have any other risk factors for HBV infection. A liver biopsy performed in September 2004 revealed a score 10 for grading and a score 6 for staging, according to the Ishak modified histology activity index. Immunohistochemistry demonstrated HbcAg positivity in rare nuclei. No standard interferon treatment was given because of the poor response of the liver flare. Both his mother and two siblings are carriers of hepatitis B virus, but he does not have any other risk factors for HBV infection.

In January 2003, the patient was diagnosed with multiple myeloma. He was referred to a hematologist because of a persistently raised serum transaminase level and a liver biopsy was performed. The patient was found to have a score 10 for grading and a score 6 for staging, according to the Ishak modified histology activity index. Immunohistochemistry demonstrated HbcAg positivity in rare nuclei. No standard interferon treatment was given because of the poor response of the liver flare. Both his mother and two siblings are carriers of hepatitis B virus, but he does not have any other risk factors for HBV infection. A liver biopsy performed in September 2004 revealed a score 10 for grading and a score 6 for staging, according to the Ishak modified histology activity index. Immunohistochemistry demonstrated HbcAg positivity in rare nuclei. No standard interferon treatment was given because of the poor response of the liver flare. Both his mother and two siblings are carriers of hepatitis B virus, but he does not have any other risk factors for HBV infection.
motherapy, the patient's aminotransferase levels remained normal and no HBV reactivation was observed by PCR.

Lamivudine was continued for a total of one year and was stopped 4 months after the bone marrow transplantation.

On admission, the patient had jaundice and the liver was tender and palpable 3 cm under the costal edge. There were no ascites or encephalopathy. Biochemical tests revealed: AST 1960 U/L (N < 45), ALT 1711 U/L (N 56-128), total bilirubin 169.8 µmol/L, conjugate bilirubin 130.7 µmol/L, prothrombin index 59 %, normal urea, normal creatinine, IgG 19.6 g/L, IgA 0.59 g/L, IgM 0.99 g/L, and a monoclonal component in the protein profile (IgG/LK 5.33 g/L). HBeAg remained undetectable, while quantitative HBV-DNA was > 10^6 copies/mL. HAV, HDV, HCV, and HIV serum markers were negative. There were no YMDD mutants.

Lamivudine was started again at a dosage of 100 mg/day, and prophylaxis against viral, fungal, and bacterial infections was also given. During the next 10 days, serum transaminases rose, peaking at 3901 U/L in AST and 2508 U/L in ALT. Total bilirubin rose to 500 µmol/L (396 µmol/L of conjugated bilirubin), and prothrombin index deteriorated to 37%.

On the 15th day in hospital, the patient developed fever (T = 38 °C), and a chest X-ray revealed bilateral pulmonary interstitial pneumonia, so intravenous antibiotic therapy was started with cephalosporin. Urinary stream culture was negative and opportunist infections were ruled out by specific blood tests. The temperature chart suggested a septic clinical picture. On the 23rd day, the patient complained of intense abdominal pain and developed signs of acute abdomen with Blumberg positivity. Abdominal X-ray failed to reveal any signs of bowel obstruction or perforation. Flat bone X-ray ruled out any reactivation of the hematological disease. Over the next 12 hours, the patient's condition worsened and renal failure developed. Post-mortem examination revealed cirrhosis with areas of necrosis and multiple organ involvement due to the septic condition: pentalobular pneumonia, bilateral pleural effusions with evidence of pus in the pleural cavity, intestinal infarction, and kidney in shock.

**Discussion**

Our patient, a bone marrow transplant recipient with HBe Ag-negative cirrhosis, experienced fatal reactivation of HBV infection 4 months after lamivudine withdrawal. Restoring lamivudine therapy failed to improve acute hepatitis and the patient died of multorgan sepsis.

Myers et al. [18] reported a case of hepatitis B and antigen-negative chronic hepatitis B reactivation in a bone marrow transplant recipient within 12 weeks after discontinuing lamivudine therapy, but in this case the acute hepatitis was promptly resolved when lamivudine therapy was started again. Table I summarizes the outcome of patients after withdrawal of lamivudine administered for prophylaxis against HBV. No sequence analysis of the HBV genome for YMDD mutations was performed in any of these reported cases. In our patient, no lamivudine resistance mutation was found, indicating that reactivation of

<table>
<thead>
<tr>
<th>Author, year, [ref]</th>
<th>N</th>
<th>Malignancy</th>
<th>HBeAg</th>
<th>Duration of lamivudine treatment after chemotherapy (weeks)</th>
<th>Follow-up after lamivudine withdrawal</th>
<th>Reactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endo, 2001, [5]</td>
<td>3</td>
<td>non-Hodgkin lymphoma</td>
<td>negative</td>
<td>40-16-16</td>
<td>17-6-7</td>
<td>no</td>
</tr>
<tr>
<td>Myers, 2001, [16]</td>
<td>1</td>
<td>BMT</td>
<td>negative</td>
<td>32</td>
<td>12</td>
<td>yes</td>
</tr>
<tr>
<td>Idilman, 2003, [10]</td>
<td>8</td>
<td>leukaemia</td>
<td>positive</td>
<td>12</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>lymphoma</td>
<td>multiple myeloma</td>
<td>21</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Shibolet, 2002, [7]</td>
<td>13</td>
<td>6 lymphoma</td>
<td>3 positive</td>
<td>1-60 days</td>
<td>21</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lymphoma</td>
<td>enophtalmitis</td>
<td>10 negative</td>
<td>1/20</td>
<td>3 negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lymphoma</td>
<td>ulcerative colitis</td>
<td>2 colon carcinoma</td>
<td>1 not done</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>breast cancer</td>
<td>8 negative</td>
<td>1 not done</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yeo, 2004, [12]</td>
<td>31</td>
<td>breast cancer</td>
<td>not done</td>
<td>8</td>
<td>not reported</td>
<td>yes (6.5%)</td>
</tr>
</tbody>
</table>

Abreviation = BMT: bone marrow transplantation.
HBV infection was due to withdrawal of lamivudine. In chronic HBV carriers with no associated malignancies, the incidence of hepatitis flares after lamivudine withdrawal is 7-19% [8] and the median ALT peak occurs 16 weeks after treatment withdrawal. Patients with cirrhosis are thought to be at greater risk of hepatitis B decompensation after a transaminase flare during an episode of hepatitis B reactivation [19]. Our patient had underlying cirrhosis which brings to mind the observation by Myers et al [18], who reported the only case of death following lamivudine withdrawal in a patient with HBV reactivation on underlying cirrhosis. The fatal outcome in our patient was due to multiorgan failure following sepsis, despite broad-spectrum prophylaxis against fungal, viral and bacterial infections.

When to discontinue lamivudine prophylaxis against HBV flares in immunosuppressed HBV carriers is still an open question. Our case and that reported by Myers et al. [18] have clear similarities: both were cirrhotic HBeAg patients with compensated cirrhosis who underwent bone marrow transplantation for malignant conditions. Long-term lamivudine therapy is needed in these patients who should be advised to continue the prophylactic treatment for at least 12 months after bone marrow transplantation. The ideal protocol of lamivudine prophylaxis for the prevention of HBV reactivation in individuals receiving chemotherapy for hematopoietic malignancies is not yet known. Close patient monitoring with liver function tests and HBV-DNA levels every month is also mandatory and lamivudine withdrawal should only be considered if there is stable HBV-DNA negativization [19]. It is also important to consider starting lamivudine again in case of HBV reactivation (corresponding to >1 log of viral load), because HBV-DNA reactivation precedes biological reactivation by at least three months. We also agree with the suggestion by Lim et al. [20] that physicians who intend to treat chronic hepatitis B with nucleoside analogues need to warn patients that stopping the treatment may have serious consequences.

REFERENCES