Lamivudine treatment enabling right hepatectomy for hepatocellular carcinoma in decompensated cirrhosis

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Abstract

A 69-year-old man was admitted to our hospital in October 2003, for further examination of two liver tumors. He was diagnosed with hepatocellular carcinoma (HCC) arising from decompensated hepatitis B virus (HBV)-related cirrhosis. Long-term lamivudine administration improved liver function dramatically despite repeated treatment for HCC. His Child-Pugh score was 9 points at start of lamivudine treatment, improving to 5 points after 1 year. His indocyanine green at 15 min after injection test score was 48% before lamivudine treatment, improving to 22% after 2 years and to 5% after 4 years. Radiofrequency ablation controlled the HCC foci and maintained his liver function. In April 2009, abdominal computed tomography revealed a tumor thrombus in the right portal vein. Since his indocyanine green test results had improved to less than 10%, we performed a right hepatectomy, which was successful. To our knowledge, there have been no documented reports of patients undergoing successful right hepatectomy for HCC arising from decompensated cirrhosis. The findings observed in our patient indicate the importance of nucleoside analogs for treating HBV-related HCC.

INTRODUCTION

The hepatitis B virus (HBV) infects more than 400 million people worldwide and is an important risk factor for the development of hepatocellular carcinoma (HCC). In Japan, about 1% of individuals in the general population are HBV carriers, accounting for about 14% of patients with liver cirrhosis and 15%-20% of those with HCC. The prognosis of patients with HCC arising from chronic liver disease is dependent not only on tumor factors but on hepatic functional reserve. Depending on patient age, liver transplantation may be a good therapeutic option in patients with poor functional reserve. Lamivudine treatment is beneficial in patients with HBV-related HCC because it contributes to improvement of remnant liver function. We describe here a patient with decompensated HBV-related cirrhosis who developed HCC. Lamivudine therapy improved liver function and enabled a right hepatectomy 5 years later.
A 69-year old man was admitted to our hospital in October 2003 for examination of two liver tumors. He had been diagnosed with hepatitis B in 1994 and treated with glycyrrhizin. His liver function deteriorated gradually, with ascites appearing in May 2001. He was first admitted to our hospital for treatment of intractable ascites (Figure 1A). Laboratory tests showed that his serum albumin (alb) concentration was 2.7 g/dL, his total bilirubin (T-Bil) was 2.8 mg/dL, his aspartate aminotransferase (AST) was 54 IU/L, his alanine aminotransferase (ALT) was 43 IU/L, and his prothrombin time (PT) was 42%. Administration of diuretic drugs was not effective, but treatment with a preparation of albumin resulted in the disappearance of ascites 1 mo later. Afterward, the ascites was kept under control by administration of diuretics. In October 2003, a computed tomographic (CT) scan of the abdomen revealed two HCCs (4.5 and 2.5 cm in diameter) in the right hepatic lobe (Figure 1B, C). Laboratory tests showed alb 2.5 g/dL, T-Bil 2.4 mg/dL, AST 152 IU/L, ALT 98 IU/L, PT 47%, indocyanine green at 15 min after injection (ICGR15) 48%, alpha-fetoprotein 444 ng/mL, and protein induced by vitamin K absence or antagonist II <10 mAU/mL. He was positive for HBe antigen, negative for HBe antibody, and had an HBV-DNA viral load of 6.7 log copies/mL. Beginning in November 2003, he was treated with 100 mg/d lamivudine. The two HCCs were treated by transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) (Figure 1D, E). Both tumors were treated successfully and the patient’s liver function recovered gradually after initiation of lamivudine treatment. In September 2005, an abdominal CT scan revealed a recurrent HCC, located near one of the previously treated tumors; this lesion was treated successfully with TACE and RFA. At this time, laboratory tests showed alb 3.7 g/dL, T-Bil 0.7 mg/dL, AST 23 IU/L, ALT 22 IU/L, PT 84% and ICGR15 22%. All HCC treatments were based on clinical practice guidelines in Japan[5], with the patient providing informed consent.

In May 2006, two HCC recurrences were detected in the right liver lobe and treated with TACE and RFA. Laboratory tests showed good liver function, alb 3.9 g/dL, T-Bil 1.1 mg/dL, AST 22 IU/L, ALT 11 IU/L, PT 95% and ICGR15 25%. In June 2007, a recurrent HCC was treated with TACE and RFA. Liver function was also excellent at this time (alb 4.0 g/dL, T-Bil 0.7 mg/dL and PT 100%). In September 2007, his viral load had again increased, with breakthrough hepatitis, and the YMDD mutation was detected. Treatment with adefovir dipivoxil plus lamivudine resulted in a gradual reduction in viral load. In December 2007, abdominal CT revealed five HCCs in the right lobe; these were treated by TACE and RFA. The patient was then treated with low-dose cisplatin and 5-fluourouracil infused through the hepatic artery. Laboratory tests showed alb 4.1 g/dL, T-Bil 1.0 mg/dL, AST 38 IU/L, ALT 30 IU/L, PT 88% and ICGR15 5%. Due to the development of a pseudoaneurysm in his hepatic artery, infusion of chemotherapy was discontinued. In March 2009, two HCCs were detected in the right lobe and were treated by RFA. Laboratory tests showed alb 3.7 g/dL, T-Bil 0.7 mg/dL, AST 35 IU/L, ALT 31 IU/L, PT 77% and ICGR15 10%. In April 2009, abdominal CT and CT angiography revealed a tumor thrombus in the right portal vein, but no lesion could be detected in the left lobe (Figure 2). Although he was diagnosed with decompensated cirrhosis, of Child-Pugh C, when first hospitalized, lamivudine treatment improved his liver function sufficiently, with an improve-

Figure 1 Computed tomography in our patient. It shows a cirrhotic pattern of the liver and massive ascites at first admission (A); Dynamic computed tomography revealed two hepatocellular carcinomas, 4.5 cm (B) and 2.5 cm (C) in diameter, in the right lobe; These two lesions were treated by transcatheter arterial chemoembolization and radiofrequency ablation (D, E).
Hepatitis B is a progressive liver disease, leading to cirrhosis and HCC. Before antiviral agents became established as effective treatments for hepatitis B, the prognosis of patients with end-stage HBV infection was generally poor. The 5-year survival rates of patients with compensated and decompensated cirrhosis have been reported to be 55%-84% and 14%, respectively. Lamivudine, an antiviral drug, is an oral nucleoside analog that inhibits DNA synthesis by terminating the nascent proviral DNA chain. It rapidly reduces both serum HBV-DNA and transaminase concentrations. Prolonged viral suppression can result in histological improvement, including the regression of fibrosis. Although a subgroup of individuals with extremely advanced disease require urgent transplantation, lamivudine treatment can achieve significant improvement in liver function and reduce the morbidity of many patients.
with decompensated cirrhosis\cite{14,19}. At present entecavir is recommended as the primary oral agent for hepatitis B because of its strong antiviral effects and low resistance rate, as well as being effective in treating decompensated cirrhosis\cite{20}. Long-term lamivudine monotherapy can induce the emergence of resistant viruses with an amino acid substitution in the YMDD motif of the viral DNA polymerase\cite{21}. Particularly in patients with decompensated cirrhosis, breakthrough hepatitis resulting from such a mutation may lead to hepatic failure\cite{22} if other antiviral drugs such as adefovir dipivoxil\cite{23,24} are not administered. Long-term treatment with lamivudine has been reported to reduce the incidence of HCC\cite{25,20}. In addition, lamivudine has been found to improve liver function\cite{27,28} and survival\cite{29} in patients with HBV-related HCC after initial treatment of HCC. We have described a patient with HCC arising from decompensated HBV-related cirrhosis. Long-term lamivudine treatment improved his remnant liver function dramatically, despite repeated TACE and RFA sessions for HCC. Although his Child-Pugh score at the start of lamivudine treatment was 9 points, it improved up to 5 points 1 year later. Moreover, he scored 48% on an ICGR15 test performed before his first treatment for HCC, but this score improved to 22% after 2 years and to 5% after 4 years, with the latter considered safe for the performance of a right hepatectomy\cite{30}.

Despite repeated RFA, the liver function of this patient was well maintained. Generally, RFA has been regarded as safe and effective for HCC, and has been found to maintain liver function\cite{31,33}. In our patient, lamivudine and RFA were effective in maintaining liver function. A previous case report described a patient with decompensated HBV-related cirrhosis, who, following lamivudine treatment, underwent a hepatectomy for HCC after liver function had improved\cite{18}. That patient, however, underwent a partial hepatectomy for a small HCC. To our knowledge, no prior report has described a successful right hepatectomy for HCC arising from decompensated HBV-associated liver cirrhosis. The findings reported in this patient indicate the importance of nucleoside analogs for treating HBV-related HCC.

In conclusion, we found that lamivudine treatment was beneficial for our patient with decompensated HBV-related cirrhosis and HCC, increasing the likelihood of treatment for HCC.

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S-Editor Gou SX  L-Editor A  E-Editor Li JY

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2590 May 28, 2012 | Volume 18 | Issue 20 |