CASE REPORT

Surgical treatment of HCC in a patient with lamivudine-resistant hepatitis B cirrhosis with adefovir dipivoxil

Takashi Akima, Masaya Tamano, Hidetsugu Yamagishi, Keiichi Kubota, Takahiro Fujimori, Hideyuki Hiraishi

Abstract

We describe a 77-year-old woman with chronic hepatitis B who became resistant to lamivudine. She was started on adefovir (10 mg daily) while still continuing lamivudine therapy. Four mo later her liver function improved and serum Hepatitis B virus (HBV)-DNA level became undetectable. Three years after the start of additional adefovir treatment, hepatocellular carcinoma (HCC) was detected and the patient underwent a successful hepatectomy. Our findings suggest that the addition of adefovir to ongoing lamivudine therapy cannot completely suppress hepatocarcinogenesis, but is useful for improving liver function in patients with lamivudine-resistant HBV-related cirrhosis, allowing HCC surgery.

Key words: Hepatitis B virus; Hepatocellular carcinoma; Hepatocarcinogenesis; Lamivudine; Adefovir dipivoxil

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most frequent malignant tumors worldwide and the third leading cause of cancer death, next to lung and stomach cancer. Hepatitis B virus (HBV) infection is one of the major causes of HCC, with interferon as one of several therapeutic options for chronic HBV infection. Recently, lamivudine, a nucleoside analogue, has been used to treat chronic HBV infection[1]. However, long-term lamivudine therapy may result in the emergence of genotypic resistance in the form of tyrosine-methionine-aspartate-aspartate (YMDD) mutations, which is occasionally associated with severe, or even fatal, breakthrough hepatitis[2,3]. Thus, there is a clear need for alternative or additional therapies. Adefovir dipivoxil (adefovir) is a nucleotide analogue that converts to an active metabolite, adefovir diphosphate[4,5]. In order to prevent breakthrough hepatitis induced by lamivudine-resistant HBV mutants, additional adefovir dipivoxil is recommended[6].

CASE REPORT

A 77-year-old Japanese female patient had been followed...
since 1977 for HBV-related chronic hepatitis. In 2002, her serum ALT level fluctuated between 100-400 IU/L (normal 4-40 IU/L), the HBV-DNA level was shown to be 6.2 log genome equivalent (LGE)/ml by transcription-mediated amplification, and alpha-fetoprotein (AFP) level was elevated to 537 ng/mL (normal upper limit 5 ng/mL). However, the desgamma carboxy prothrombin (DCP) level was within normal limits. Abdominal ultrasonography and dynamic computed tomography (CT) revealed no evidence of HCC. From December 2002, the patient started to receive lamivudine at a dose of 100 mg per day. The serum ALT and AFP levels decreased to the normal range, HBV-DNA decreased to undetectable levels. After 30 mo of lamivudine treatment, the serum HBV-DNA level increased rapidly to 5.1 LGE/mL with serum ALT elevation (127 IU/L). The lamivudine-resistant YVDD mutant strain of HBV was detected. The patient was then treated with adefovir at a dose of 10 mg daily in addition to lamivudine from July 2005.

Abdominal ultrasonography and dynamic CT were performed every 6 mo. In July 2008, dynamic CT showed a tumor in segment 8 of the liver measuring 10 mm in diameter. The patient was admitted for further examination in September 2008. Digital subtraction angiography showed a tumor staining 20 mm in diameter (Figure 1A), CT during arterial portography showed a perfusion defect in segment 8 (Figure 1B), and CT during hepatic arteriography showed a hypervascular lesion in the corresponding region (Figure 1C). The tumor was diagnosed typical stage I HCC. Laboratory data upon admission is shown in Table 1. The patient's Child-Pugh grade was A. Since the tumor was not detected by ultrasonography, percutaneous ethanol injection and radiofrequency ablation were not performed. After outlining the treatment plan, including surgery and transcatheter arterial chemomobilization (TACE), the patient opted to undergo surgery and subsegmentectomy was successfully performed in October 2008. The tumor was a nodular lesion measuring 16 mm × 13 mm. Microscopically, the tumor was a moderately differentiated HCC with a trabecular pattern (Figure 2A). The non-tumorous liver tissue showed cirrhosis (Figure 2B). HBs Ag and HBc Ag were not detected by immunohistological staining in either the tumorous or non-tumorous portions.

**DISCUSSION**

The epidemiological association of HBV with HCC is well established. In recent studies, it was revealed that HBsAg carriers have a 25-37 fold increased risk of developing HCC compared to non-infected people.

In 1998, lamivudine was approved as the first nucleotide analogue treatment of chronic hepatitis B[7]. However, drug-resistant mutants arise over the duration of lamivudine treatment, at 12.5% after 1 year, 43.8% after 3 years, and 62.5%-70.2% after 5 years[8,9]. For preventing breakthrough hepatitis induced by lamivudine-resistant HBV mutants, additional adefovir dipivoxil...
Table 1 Laboratory data on admission

| Blood chemistry | Value | Hematological analysis | Value | Viral markers | Value | Coagulation | Value | Tumor markers | Value |
|-----------------|-------|------------------------|-------|---------------|-------|-------------|-------|---------------|-------|
| TP (g/dL)       | 7.8   | WBC (× 103/L)          | 3.60  | HBe Ag (IU/mL) | 5.56  | PT (%)      | 67    | AFP (ng/dL)   | <5    |
| Alb (g/dL)      | 4.1   | RBC (× 106/L)         | 4.59  | Hbs Ab (mIU/mL) | 1.20  |             |       | PIVKA-II (mAU/mL) | 22    |
| AST (IU/dL)     | 33.0  | Hb (g/dL)               | 13.00 | Hbe Ag (S/CO)  | 0.30  |             |       |               |       |
| ALT (IU/dL)     | 28.0  | Ht (%)                  | 40.60 | Hbe Ab (%Inh)  | 89.60 |             |       |               |       |
| LDH (IU/dL)     | 168.0 | Plt (× 103/L)          | 8.80  | HBV-DNA        |       |             |       |               |       |
| ALP (IU/dL)     | 313.0 |                        |       |               |       |             |       |               |       |
| GGT (IU/dL)     | 30.0  |                        |       |               |       |             |       |               |       |
| T-bil (mg/dL)   | 0.6   |                        |       |               |       |             |       |               |       |
| ZTT (KIU)       | 8.7   |                        |       |               |       |             |       |               |       |

TP: total protein; Alb: albumin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactic dehydrogenase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transpeptidase; T-bil: total bilirubin; ZTT: zinc turbidity test; WBC: white blood cells; RBC: red blood cells; Hb: hemoglobin; Ht: hematocrit; Plt: platelets; PT: prothrombin time; AFP: alpha-fetoprotein; PIVKA-II: protein induced by vitamin K absence or antagonist-II.

(10 mg daily) has been recommended\(^1\) as it is more effective than switching to adefovir monotherapy and has fewer chances of developing drug-resistant mutants\(^11,12\). Lamivudine-resistant patients treated with lamivudine add-on adefovir can achieve both an excellent virological and biochemical response, but cannot completely suppress hepatocarcinogenesis\(^11,14\). It was reported that HCC development was observed in 7.3% of patients who received long-term adefovir add-on lamivudine over periods of up to 5 years. Serum ALT levels (≥ 70 IU/L), YMDD mutants, cirrhosis and age were independent factors for the development of HCC\(^15\). In the present case, serum ALT levels were within the normal range after receiving adefovir add-on lamivudine therapy, although the YMDD mutant was present. Furthermore, the patient was a senior citizen and her liver was cirrhotic at the start of lamivudine therapy. Therefore, this patient was at high hepatocarcinogenesis risk in the adefovir add-on lamivudine therapy group. HCC was detected about three years after starting additional adefovir treatment. The patient’s clinical status and liver function were sufficiently improved when HCC was detected, allowing for successful surgical resection.

In conclusion, our experience suggests that adefovir add-on lamivudine therapy cannot completely suppress hepatocarcinogenesis, but is effective for reversing hepatic decompensation. The continuation of the combined lamivudine and adefovir treatment maintains stable liver function, permitting subsequent surgery for HCC.

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S- Editor Zhang HN  I- Editor Hughes D  E- Editor Liu N