A Case of HCV-Associated Liver Cirrhosis Who Developed Hepatocellular Carcinoma Twice After Sustained Viral Clearance with Direct-Acting Antiviral Agents

Yo Fujimoto1, Yumi Kusano1, Toshitsugu Suda1, Osamau Okawa1, Tomohiro Kitagawa1, Naohiko Tokutomi1, Ryosaku Shirahashi1, Shinichi Ban2, and Masaya Tamano1

1Department of Gastroenterology, Dokkyo Medical University Saitama Medical Center, Japan
2Department of Pathology, Dokkyo Medical University Saitama Medical Center, Japan

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*Corresponding author: Masaya Tamano, Department of Gastroenterology, Dokkyo Medical University Saitama Medical Center, 2-1-50 Minami-Koshigaya, Koshigaya-shi, Saitama 343-8555, Japan, Tel: 81-48-965-1111; Fax: 81-965-1169; E-mail: mstamano@dokkyomed.ac.jp

Abstract

Background: Oral direct-acting antiviral (DAA) therapy without interferon (IFN) has been developed since 2014 to treat hepatitis C. However, there have been few reports of the suppression of cancer after DAA treatment. The case of a patient with hepatitis C-related cirrhosis who developed cancer twice after sustained virological response (SVR) with DAs is reported.

Case Report: The patient was a 65-year-old female dentist with chronic hepatitis C (genotype 1b) who was treated with peginterferon monotherapy in 2003, without achieving viral clearance. In 2014, she presented seeking DAA therapy. HCV RNA was 5.6 log IU/mL. On abdominal ultrasound (US), her liver showed cirrhosis with no neoplastic lesions. Treatment with daclatasvir/asunaprevir was started, and her blood was negative for HCV RNA four weeks later. Treatment ended at 24 weeks, with no hepatic neoplasms on US. Twenty-four weeks later, HCV RNA remained negative, and no hepatic neoplasms were seen on US. Nine months after treatment ended, a weekly hyperechoic, 1.2 cm mass was found in liver segment four on US, hepatocellular carcinoma (HCC) was confirmed on gadolinium ethoxybenzyl diethylene triamine penta acetic acid magnetic resonance imaging, and partial hepatectomy was performed. Eighteen months after treatment ended, a 2.3 cm tumor was found in liver segment six. US-guided biopsy was performed, along with RFA, and moderately differentiated hepatocellular carcinoma was diagnosed.

Conclusions: The present patient appeared to have been in a high-risk group with older age and advanced fibrosis. However, cancer occurring twice in a short time after achieving SVR24 is very rare.

Keywords: Hepatitis C; Direct-acting antiviral agents; Hepatocellular carcinoma

Introduction

Treatment for hepatitis C has progressed from interferon (IFN) therapy with IFN and ribavirin (RBV) and then 3-drug combination therapy with DAAs. However, there are many adverse effects with IFN treatment, including fever, joint pain, loss of appetite, and hair loss, making treatment in older people difficult.

Oral DAA therapy without the use of IFN has been developed since 2014, and the treatment of hepatitis C has progressed rapidly. With DAAs, the side effects are much milder than with IFN treatment, and a high rate of sustained virological response (SVR) is obtained [1–5]. There are few reports, however, on the suppression of cancer after treatment with DAAs. The case of a patient with hepatitis C-related cirrhosis who developed cancer twice after SVR with DAAs is reported.

Case Report

At our hospital in 2003, she presented seeking DAA therapy. HCV RNA was 5.6 log IU/mL. On abdominal ultrasound (US), her liver showed cirrhosis, but no neoplastic lesions were seen. The data were consistent with compensated cirrhosis. Y93 and L31 in the NS5A were wild type. On abdominal ultrasound (US), her liver showed cirrhosis with no neoplastic lesions. Hematocrit and platelet counts were normal. The data were consistent with compensated cirrhosis. The viral RNA was 5.6 log IU/mL. A 1.2 cm mass was found in liver segment four on US, which was confirmed on gadolinium ethoxybenzyl diethylene triamine penta acetic acid magnetic resonance imaging, and partial hepatectomy was performed. Eighteen months after treatment ended, a 2.3 cm tumor was found in liver segment six. US-guided biopsy was performed, along with RFA, and moderately differentiated hepatocellular carcinoma was diagnosed.

Conclusions: The present patient appeared to have been in a high-risk group with older age and advanced fibrosis. However, cancer occurring twice in a short time after achieving SVR24 is very rare.

Keywords: Hepatitis C; Direct-acting antiviral agents; Hepatocellular carcinoma

Blood Test Results

<table>
<thead>
<tr>
<th>Blood Test Results</th>
<th>TP 6.8 g/dl</th>
<th>WBC 5200 x 10³/μl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alb</td>
<td>4.23 g/dl</td>
<td>RBC 527 x 10³/μl</td>
</tr>
<tr>
<td>T Bil</td>
<td>0.75 mg/dl</td>
<td>Hb 14.9 g/dl</td>
</tr>
<tr>
<td>AST</td>
<td>37 IU/l</td>
<td>Ht 44.0 %</td>
</tr>
<tr>
<td>ALT</td>
<td>35 IU/l</td>
<td>Ptk 7.5 x 10³/μl</td>
</tr>
<tr>
<td>LDH</td>
<td>263 IU/l</td>
<td>PT % 115.0 %</td>
</tr>
<tr>
<td>ALP</td>
<td>210 IU/l</td>
<td>yGT P 30 IU/l</td>
</tr>
<tr>
<td>BUN</td>
<td>20 mg/dl</td>
<td>HBs antigen</td>
</tr>
<tr>
<td>Cre</td>
<td>0.59 mg/dl</td>
<td>HBs antibody</td>
</tr>
<tr>
<td>Na</td>
<td>141 mEq/l</td>
<td>Hbc antibody</td>
</tr>
<tr>
<td>K</td>
<td>4.2 mEq/l</td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>108 mEq/l</td>
<td>HCV RNA 5.6 log IU/mL</td>
</tr>
</tbody>
</table>

Table 1: Blood test results at the first medical examination.

Patient

The patient was a 65-year-old woman who was a dentist. Her family and medical histories were both unremarkable. She had no history of alcohol or drug use. She had been treated with peginterferon monotherapy for chronic hepatitis C at another hospital in 2003, but viral clearance was not achieved, and, in 2014, she was examined at our hospital seeking DAA therapy.

Blood test results are shown in table 1. Her hepatitis C virus (HCV) genotype was 1b, and the RNA amount was 5.6 log IU/mL. A mild elevation of transaminase levels and decreases in albumin and platelet counts were seen. The data were consistent with compensated cirrhosis. Y93 and L31 in the NS5A were wild type. On abdominal ultrasound (US), her liver showed cirrhosis, but no neoplastic lesions were seen.

Treatment with daclatasvir/asunaprevir (DCV/ASV) was started in November 2014, and four weeks later her blood was negative for HCV RNA. Treatment was ended at 24 weeks with no adverse effects, and no neoplastic lesions were seen in the liver on US at the time of treatment completion. Twenty-four weeks after the end of treatment, she was still negative for HCV RNA, and no neoplastic lesions were seen in the liver on US at that time.

In February 2016 (nine months after the end of treatment), a weekly hyperechoic, 1.2 cm mass was seen in segment four of the
liver on US (Figure 1), and gadolinium ethoxy benzylidiethylene triamine penta acetic acid magnetic resonance imaging (EOB-MRI) showed early enhancement of the same mass, with a defect in the hepatobiliary phase. Hepatocellular carcinoma (HCC) was diagnosed (Figure 2). Since the mass was directly beneath the diaphragm, radiofrequency ablation (RFA) was considered difficult, and partial hepatectomy was performed.

Figure 3 shows images of the tumor tissue portion on the left and non-tumor portion on the right. A nodular mass was seen with no formation of a fibrous capsule, with well-differentiated hepatocellular carcinoma consisting of narrow cord-like structures with 1 or 2 layers and slit-like sinusoidal vessels. On magnified images of non-tumor liver tissue, there were mixed large and small nodules, with cirrhosis with narrow septa.

In November 2016 (18 months after the end of treatment), a 2.3 cm tumor thought to be ectopic recurrence of HCC in segment six of the liver was seen on follow-up EOB-MRI (Figure 4). US-guided biopsy of the same site was performed, and RFA was performed at the same time. Increased nuclear density, nuclear atypia, and large, indistinct cord-like structures were seen in the biopsy tissue, and moderately differentiated hepatocellular carcinoma was diagnosed (Figure 5).

AFP and PIVKA-II levels were both within the reference range before treatment, at the end of treatment, at the time that the first cancer was found, and at the time that the second cancer was found.
Discussion

Conventional IFN therapy is effective in inhibiting hepatocarcinogenesis, and patients who achieve SVR have a significantly lower rate of developing hepatocellular carcinoma than those who do not [6,7]. Nevertheless, carcinogenesis occurring long after achieving SVR has been reported, and screening according to carcinogenesis risk is needed [8]. Asahina, et al. reported that high AFP levels after IFN therapy, high post-treatment levels of ALT, male sex, older age, advanced fibrosis, hepatic steatosis, hypoalbuminemia, and failure to achieve SVR were factors contributing to the development of hepatic cancer after IFN therapy. Post-treatment AFP of ≥ 6 ng/ml and ALT of ≥ 40 IU/L in particular are reported to be independent carcinogenesis factors whether or not SVR is achieved [9].

Am much higher SVR rate is obtained with DAA therapy than with IFN therapy. The cancer-inhibiting effect of DAs was reported to be the same as in an IFN treatment group [10], but there have also been reports that DAA therapy facilitates the recurrence of HCC after a cure has been achieved [11,12]. Thus, no consensus has been reached. There are no reports on factors that predict cancer development following treatment with DAs.

This patient was a woman in whom post-treatment AFP and ALT levels were low, and albumin was in the standard range. In accordance with cancer prediction following IFN therapy, she may be judged to have been in a high-risk group with older age and advanced fibrosis. However, it is very rare to see cancer occur twice in a short time after achieving SVR 24.

It is important that a HCC can persist latent for a long time. However, the ultrasonography was performed repeatedly by a board-certified fellow of the Japan Society of Ultrasonics in Medicine before her initial cancerogenesis. And, at the time of initial cancerogenesis, it was confirmed by EOB-MRI any place other than S4 that there was not a tumor. So, we diagnosed that she developed hepatocellular carcinoma twice after sustained viral clearance with direct-acting antiviral agents.

Conflict of Interest

No conflict of interest to declare.

References


*Corresponding author: Masaya Tamano, Department of Gastroenterology, Dokkyo Medical University Saitama Medical Center, 2-1-50 Minami-Koshigaya, Koshigaya-shi, Saitama 343-8555, Japan, Tel: 81-48-965-1111; Fax: 81-965-1169; E-mail: mstamano@dokkyomed.ac.jp

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