Peritoneal Dissemination of Hepatocellular Carcinoma Treated with a Combination Therapy of Interferon-alpha-2b and Oral Tegafur/Uracil

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Abstract

We encountered a case of peritoneal dissemination of hepatocellular carcinoma, successfully treated with a combination therapy of interferon-alpha-2b and oral tegafur/uracil. A 67-year-old Japanese man who underwent a hepatectomy developed peritoneal dissemination. A combination therapy of subcutaneous interferon-alpha-2b and intravenous 5-fluorouracil was started. Four weeks later, he felt severe general fatigue and nausea, and intravenous 5-fluorouracil was replaced with oral tegafur/uracil. At 3 months after the initiation of chemotherapy, enhanced computed tomography showed markedly reduced peritoneal dissemination. A combination therapy of interferon-alpha-2b and oral tegafur/uracil is facile and may be effective for extrahepatic metastasis of hepatocellular carcinoma.

Key words: systemic chemotherapy, extrahepatic metastasis, 5-fluorouracil

In this report, we describe a Japanese man who developed peritoneal dissemination of hepatocellular carcinoma after hepatectomy, in whom marked tumor regression was found with a combination therapy of interferon-alpha-2b and oral tegafur/uracil.

Case Report

A 67-year-old Japanese man was admitted to Okayama University Hospital with hepatocellular carcinoma in February 2005. Hepatitis C virus antibody was positive, while hepatitis B surface antigen was negative. Serum levels of alpha-fetoprotein and des-gamma-carboxy prothrombin were markedly elevated (Table 1). Enhanced computed tomography showed a hepatic mass with early-phase hyperattenuation and late-phase hypoattenuation, measuring 8.5×5.4 cm in the posterior segment of the liver (Fig. 1A, B). No ascites was found. In March 2005, a posterior segment resection was performed. Histological examination revealed a moderately differentiated hepatocellular carcinoma arising in cirrhotic hepatic parenchyma (Fig. 1C, D). The postopera-
Table 1. Laboratory data at the diagnosis of hepatocellular carcinoma and at the diagnosis of peritoneal dissemination

<table>
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<tr>
<th>Test</th>
<th>Date</th>
<th>Value 1</th>
<th>Value 2</th>
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<tr>
<td>White blood cell count (mm³)</td>
<td>February 2005</td>
<td>5700</td>
<td>3900</td>
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<td>Hemoglobin (g/dL)</td>
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<td>15.4</td>
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<td>Platelet count (x 10³/mm³)</td>
<td>February 2005</td>
<td>281</td>
<td>187</td>
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<td>Albumin (g/dL)</td>
<td>June 2005</td>
<td>3.7</td>
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<td>Total bilirubin (mg/dL)</td>
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<td>1.04</td>
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<td>Aspartate aminotransferase (IU/L)</td>
<td>June 2005</td>
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<td>95</td>
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<td>Alanine aminotransferase (IU/L)</td>
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<td>Creatinine (mg/dL)</td>
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<td>Prothrombin time (INR)</td>
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<td>Alpha-fetoprotein (ng/mL)</td>
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<td>54535</td>
<td>45562</td>
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<td>Des-gamma-carboxy prothrombin (mAU/mL)</td>
<td>June 2005</td>
<td>2576</td>
<td>260</td>
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</table>

Discussion

Recently, the efficacy of chemotherapy using interferon-alpha for advanced hepatocellular carcinoma has been reported (5, 7). Especially, in patients with major portal vein tumor thrombosis and without extrahepatic metastasis, the efficacy of a combination therapy of subcutaneous interferon-alpha and intra-arterial 5-fluorouracil is reported to be a 44% response rate (complete response rate and partial response rate) and 15% complete response rate (6). However, in patients with extrahepatic metastasis, the efficacy of systemic chemotherapy using interferon-alpha is uncertain. Miyamoto et al (8) reported a case of hepatocellular carcinoma with multiple intrahepatic as well as pulmonary and bone metastases, who was successfully treated by a combination therapy of interferon-alpha and oral tegafur/uracil. In the present case, peritoneal dissemination of hepatocellular carcinoma without intrahepatic recurrence appeared, and partial response was achieved with a combination therapy of interferon-alpha-2b and oral tegafur/uracil. Systemic chemotherapy using interferon-alpha may be effective for extrahpatic metastasis.

Several anti-cancer drugs were administered to the present case. The serum levels of both alpha-fetoprotein and des-gamma-carboxy prothrombin decreased after the combination therapy of interferon-alpha-2b and oral tegafur/uracil for four weeks. Furthermore, during the combination therapy of interferon-alpha-2b, oral tegafur/uracil, and intravenous cisplatin, the increasing tendency of serum level of for alpha-fetoprotein, but not des-gamma-carboxy prothrombin, decreased. Thus, in the present case, the combination therapy of interferon-alpha-2b and intravenous 5-fluorouracil was considered effective, while the efficacy of the combination therapy of interferon-alpha-2b and intravenous 5-fluorouracil was uncertain.

It has been controversial whether oral administration of tegafur/uracil improves the prognosis of patients with advanced unresectable hepatocellular carcinoma (9, 10). However, recently, the effectiveness of combination chemotherapy using oral tegafur/uracil has been reported (11, 12).
Figure 1. Demonstration of hepatocellular carcinoma by enhanced computed tomography and histological features of the non-tumorous lesion and tumorous lesion. A: Enhanced computed tomography shows a hepatic mass with early-phase hyperattenuation, measuring 8.5 × 5.4 cm in the posterior segment of the liver (arrow). B: The hepatic mass shows late-phase hypoattenuation (arrow). C: Histological features of the resected non-tumorous lesion shows cirrhosis (HE stain, ×25). D: Histological features of the resected tumorous lesion shows a moderately differentiated hepatocellular carcinoma with an increased nuclear-cytoplasm ratio and nuclear atypia, which proliferated in a trabecular pattern (HE, ×100).

Tegafur/uracil consists of tegafur and uracil in a 1:4 molar ratio. Tegafur is metabolized to 5-fluorouracil in the liver, and uracil potentiates the efficacy of tegafur by inhibiting dihydropyrimidine dehydrogenase activity. Hepatocellular carcinoma is reported to have a relatively high dihydropyrimidine dehydrogenase activity (13). Furthermore, oral tegafur/uracil is facile. Thus, the administration of tegafur/uracil to patients with hepatocellular carcinoma may be reasonable.

In a recent report from Japan, major extrahepatic metastasis sites are confirmed to be lung, bone, and lymph node (3). Peritoneal dissemination is rare and usually is a consequence of rupture of the primary tumor (3, 14). Furthermore, peritoneal dissemination is reported to be a complication of hepatectomy, microwave coagulation therapy, ethanol injection therapy, and percutaneous needle biopsy (15-21). In the present case, there was no history of rupture of the primary tumor, and the interval from hepatectomy to the detection of peritoneal dissemination was 3 months. We speculate that, in our case, peritoneal dissemination might have been the result of intraoperative contamination. On the other hand, surgical treatment is recommended for peritoneal dissemination of hepatocellular carcinoma, based on the resistance of extrahepatic metastasis to systemic chemotherapy (16). However, we consider that outcomes of resection for peritoneal dissemination may depend on the state of tumors and the skills of surgeons.

The present patient developed general fatigue and nausea during the chemotherapy using intravenous 5-fluorouracil or cisplatin. On the other hand, during the combination therapy of interferon-alpha-2b and oral tegafur/uracil, no severe adverse events occurred, and white blood cell and neutrophil counts were maintained at ≥3000/mm³ and ≥1500/mm³, respectively. He died of necrotizing cellulitis; however, the association between necrotizing cellulitis and the chemotherapy was uncertain.

In conclusion, a combination therapy of interferon-alpha-2b and oral tegafur/uracil is facile and may be effective for extrahepatic metastasis of hepatocellular carcinoma. However, the efficacy of oral tegafur/uracil for patients with advanced unresectable hepatocellular carcinoma has been controversial. On the other hand, the efficacy of a combination
Figure 2. Patient’s clinical course. OP, operation; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin, IFN-\(\alpha\)-2b, interferon-alpha-2b; 5-FU, 5-fluorouracil; UFT, tegafur/uracil; CDDP, cisplatin.

Figure 3. Demonstration of hepatocellular carcinoma disseminated to the peritoneum by computed tomography before and after the chemotherapy. A: Computed tomography shows the second (white arrow) and the third (black arrow) largest lesions of peritoneal dissemination before the chemotherapy, measuring 1.1 \(\times\) 1.0 cm and 1.0 \(\times\) 0.8 cm, respectively. B: Computed tomography shows the largest lesion of peritoneal dissemination before the chemotherapy, measuring 2.6 \(\times\) 2.1 cm (arrow). C: Computed tomography shows complete disappearance of disseminated lesions after the chemotherapy (arrow). D: Computed tomography shows a reduced disseminated lesion after the chemotherapy, measuring 1.6 \(\times\) 1.3 cm (arrow).
therapy of interferon-alpha and intra-arterial 5-fluorouracil for patients with major portal vein tumor thrombosis has been reported. We consider that, in order to compare the efficacy of a combination therapy of interferon-alpha and oral tegafur/uracil to that of interferon-alpha and intravenous 5-fluorouracil, a prospective study for patients who develop extrahepatic metastasis of hepatocellular carcinoma is warranted.

References