A Complete Response Induced by 21-day Sorafenib Therapy in a Patient with Advanced Hepatocellular Carcinoma

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Abstract

The response rate and overall survival after sorafenib administration in patients with advanced hepatocellular carcinoma are unsatisfactory. We herein present the case of a 65-year-old man with multiple lung metastases of hepatocellular carcinoma. Because the patient had liver cirrhosis of Child-Pugh B accompanied by pancytopenia, sorafenib administration was initiated at a dose of 400 mg daily. Although he received sorafenib for only 21 days, the patient exhibited complete regression of the tumors. There was no clinical evidence of recurrence without the administration of anticancer treatment. It is unique that short-term sorafenib treatment achieved a complete response.

Key words: sorafenib, complete response, hepatocellular carcinoma


Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide (1). Resection and local ablation therapy, including radiofrequency ablation and percutaneous ethanol injection (PEI), are curative treatments for HCC (2-4). Transcatheter arterial chemoembolization (TACE) or transcatheter arterial embolization (TAE) are recommended as the first-line non-curative therapies for patients with large or multifocal unresectable HCC without vascular invasion or extrahepatic spread (4). However, the majority of patients develop recurrence or metastasis following these treatments. The prognosis of patients with advanced HCC remains poor. In addition, liver transplantation is not recommended for such patients due to the high risk of recurrence and poor outcome. Chemotherapy is recognized to be a palliative treatment for advanced HCC. Sorafenib, an oral multikinase inhibitor that targets Raf kinase and receptor tyrosine kinases (5), was found to prolong the overall survival and time to progression with manageable toxicity compared to a placebo in two phase III trials (6, 7). Therefore, sorafenib is now recommended as the first-line option in patients with a preserved liver function in whom resection, transplantation, local ablation therapy or TACE (TAE) are not effective. However, systemic chemotherapy is associated with unsatisfactory results in terms of response and survival in patients with advanced HCC. We herein report the case of a patient with multiple metastases of HCC that regressed following short-term treatment with sorafenib.

Case Report

The patient was diagnosed with chronic hepatitis C in 1988 when he was 43 years of age. In August 2001, at 56 years of age, a tumor in segment 3 of the patient’s liver displayed the typical computed angiographic pattern of HCC, and TACE was performed. Subsequently, recurrence of HCC was observed, and the patient underwent PEI four times and TACE 10 times. In June 2010, computed tomography (CT) revealed invasion of the cancer into the inferior vena cava (IVC), and thus TAI with miriplatin hydrate (Dainippon Sumitomo Pharma Co., Ltd.) was administered. The cancer persisted, and the patient received particle beam radiation...
therapy for the cancer invading the IVC. In November 2010, multiple recurrence of HCC was observed in the liver and lungs. Because the patient had liver cirrhosis of Child-Pugh B accompanied by pancytopenia, we did not initiate sorafenib treatment and considered that controlling the HCC in the liver first would be better for the patient’s prognosis. TACE was performed in December 2010 for recurrence of the HCC in the liver. In February 2011, when the patient was 65 years of age, CT revealed that the multiple metastases in the lungs would determine the patient’s prognosis (the upper side of Fig. 1). On admission, laboratory examinations revealed the following values: aspartate aminotransferase (AST), 57 IU/L; alanine aminotransferase (ALT), 44 IU/L; bilirubin, 0.5 mg/dL; albumin, 2.8 g/dL; and prothrombin international normalized ratio (PT-INR), 1.18. The patient had severe ascites uncontrolled by furosemide treatment at a high dose (more than 80 mg/day), and no coma (Child-Pugh class B) was observed. Due to a low platelet count (36,000/μL), sorafenib administration was initiated at a dose of 400 mg daily on March, 2011. However, the sorafenib administration was discontinued on day 21 because the patient’s general condition deteriorated, namely, the severe ascites worsened, a grade I hepatic coma appeared and the performance status (PS) was 3 immediately after starting the therapy. The patient was sent to a hospice to receive palliative care on March, 2011. Two months after the discontinuation of sorafenib therapy, the PS improved, and the patient was discharged from the hospice. The levels of alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP) at the start of sorafenib treatment were 55,607 ng/mL and 11,302 mAU/mL, respectively. After five months of treatment, these levels decreased to 5 ng/mL and 23 mAU/mL, respectively (Fig. 2). CT revealed that lung metastasis was no longer present (the lower side of Fig. 1). The administration of sorafenib was not started again due to the patient’s poor liver function. In April 2012, 13 months after treatment, the patient died of acute myocardial infarction, and there was no clinical evidence of intra- or extrahepatic recurrence without any anticancer treatment.

Discussion

This case is a rare case of a complete remission following treatment with sorafenib in a patient with advanced HCC confirmed on the basis of imaging and the levels of tumor markers. Sorafenib has become the standard treatment option in patients in whom resection, transplantation, local ablation therapy and TACE cannot be performed. However, systemic chemotherapy with sorafenib is thought to be unsatisfactory in terms of response and survival in advanced HCC patients. Sorafenib therapy did not achieve a complete response in 299 patients in the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) study or 150 patients in the Asian Pacific study; the partial response rates were 2.0% and 3.3%, respectively (6, 7). Only a few studies have reported a complete response in HCC patients receiving sorafenib treatment (8-16). We listed these in order of the time to cessation (Table). According to reports of a complete response in HCC patients receiving sorafenib treatment, the duration of sorafenib administration ranged from a minimum of four to 18 months. Our case is unique because the patient was treated with sorafenib for only 21 days. Our patient achieved a complete response within three months. We were unable to determine the exact time to the complete response because the patient was sent to a hospice to receive palliative care without undergoing an evaluation of the effect of sorafenib.

The HCC observed in this patient may have regressed spontaneously. Spontaneous regression is defined by Everson and Cole as involution of a malignant tumor without the application of a specific therapy (17, 18).Spontaneous regression of malignant tumors is estimated to occur in one out of 60,000-100,000 patients. Half of such patients have renal cell carcinoma, neuroblastoma or malignant melanoma, and spontaneous regression of HCC is extremely rare (19).

Sorafenib is a multikinase inhibitor that targets Raf kinase, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), Flt-3 and c-Kit receptor tyrosine kinase. It is metabolized by CYP3A4, CYP2B6, CYP2C9, CYP2C8, UGT1A1, UGT1A9 and so on (20). The sensitivity of the response to molecular target drugs is usually correlated with particular
Table. CR in HCC Patients Receiving Sorafenib Treatment

<table>
<thead>
<tr>
<th>Author</th>
<th>Gender</th>
<th>Age</th>
<th>Etiology</th>
<th>Distant Metastasis</th>
<th>Time to cessation</th>
<th>Time to CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hagihara</td>
<td>M</td>
<td>65</td>
<td>HCV</td>
<td>Lung</td>
<td>21 days</td>
<td>unknown</td>
</tr>
<tr>
<td>Inuzuka</td>
<td>F</td>
<td>76</td>
<td>HCV</td>
<td>Lung</td>
<td>4 months</td>
<td>3 months</td>
</tr>
<tr>
<td>So</td>
<td>M</td>
<td>78</td>
<td>Hemo-chromatosis</td>
<td>Lung</td>
<td>6 months</td>
<td>5 months</td>
</tr>
<tr>
<td>Curtit</td>
<td>M</td>
<td>56</td>
<td>HCV</td>
<td>No</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Irtan</td>
<td>M</td>
<td>59</td>
<td>Hemo-chromatosis</td>
<td>Lung node, Omentum</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Wang</td>
<td>M</td>
<td>74</td>
<td>HCV</td>
<td>No</td>
<td>8 months</td>
<td>8 months</td>
</tr>
<tr>
<td>Kudo</td>
<td>M</td>
<td>68</td>
<td>HBV</td>
<td>Lung</td>
<td>none</td>
<td>2 months</td>
</tr>
<tr>
<td>Chelis</td>
<td>M</td>
<td>69</td>
<td>HBV, HIV</td>
<td>Lung node</td>
<td>none</td>
<td>6 months</td>
</tr>
<tr>
<td>Sacco</td>
<td>M</td>
<td>84</td>
<td>HCV</td>
<td>No</td>
<td>none</td>
<td>6 months</td>
</tr>
<tr>
<td>Yeganeh</td>
<td>M</td>
<td>54</td>
<td>HBV</td>
<td>Lung</td>
<td>none</td>
<td>18 months</td>
</tr>
</tbody>
</table>

Figure 2. Changes in the levels of alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP) over the past two years.

Biomarkers. There are some successful examples, as is the case with erlotinib/gefitinib in lung cancer patients with the epidermal growth factor receptor (EGFR) mutation (21), trastuzumab in breast cancer patients with HER2 amplification (22), cetuximab in colorectal cancer patients with the K-ras wild-type expression (23) and so on. Unfortunately, with respect to hepatocellular carcinoma, no biomarkers predicting the response to sorafenib have been identified in large-scale studies (24). This is due to the heterogeneity of hepatocellular carcinoma (25, 26). In some particular situations, such as in patients with a small tumor burden, favorable outcomes may be achieved, in which tumors are accidentally sensitive to sorafenib. The drug sensitivity profile may change if there exists a certain genetic polymorphism or certain interactions with other drugs. The plasma concentration of sorafenib in this patient was different for an unknown reason. The Barcelona-Clinic Liver Cancer staging classification and treatment schedule proposed by the American Association for the Study of Liver Disease recommend that the treatment method for hepatocellular carcinoma be determined based on the progression of hepatocellular carcinoma, the liver function and the performance status. Although pulmonary metastasis existed in this case, the HCC in the patient’s liver and inferior vena cava were almost controlled with TACE, transcatheter arterial infusion chemotherapy (TAI) and particle beam radiation therapy, and the number of tumors was reduced. Before administering sorafenib medication, every effort should be made to reduce the number of tumors. It is also very important to improve the liver function, which affects the applicability of treatment. If tumors in the liver are controlled and the liver function is improved, it is worth prescribing sorafenib in patients for only a short time. The immune system plays a role in tumor regression. Vascular endothelial growth factor (VEGF) inhibits the differentiation and maturation of dendritic cells and thus plays a potential immunosuppressive role (27). Sorafenib targets VEGF-mediated angiogenesis (5), which suggests the role of sorafenib in upregulating the immune system (28). Immunological factors may play an important role in this rare phenomenon; however, to date, this role remains.
incompletely understood (29).

**Conclusion**

We experienced a rare case of a complete response following short-term treatment with sorafenib in a patient with advanced HCC with lung metastasis. Further studies are required to elucidate the precise mechanisms of this phenomenon. It is important to accumulate and carefully analyze these rare cases in order to explore the development of new therapies for advanced HCC.

**The authors state that they have no Conflict of Interest (COI).**

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**References**