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Rapid Regression of Advanced Hepatocellular Carcinoma Associated with Elevation of Des-Gamma-Carboxy Prothrombin after Short-Term Treatment with Sorafenib – A Report of Two Cases

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Key Words
Hepatocellular carcinoma · Sorafenib · Rapid regression · Des-gamma-carboxy prothrombin · Biomarker

Abstract
Background: Sorafenib is the first molecular-targeted agent that is effective for advanced hepatocellular carcinoma (HCC), with prolongation of survival. However, a complete response is very rare, and rapid regression of HCC after short-term treatment with sorafenib has not been reported previously.
Case Reports: We describe 2 patients with advanced multiple HCC who received sorafenib for short periods of 1 or 2 weeks, respectively. Longer treatment was precluded by the development of hepatic failure as an adverse event of sorafenib.
Results: HCC rapidly regressed, and both patients had a partial response (PR), despite short-term treatment. Furthermore, an early elevation of des-gamma-carboxy prothrombin (DCP) was temporarily seen in both patients, with no elevation of alpha-fetoprotein.
Conclusions: Sorafenib can induce rapid regression of advanced HCC even after short-term treatment, and the initial response of HCC was identical in both patients. Since early elevation of DCP was observed in our patients with PR, DCP might be a predictive biomarker of anti-tumor response. Further studies are required to clarify the mechanisms underlying the effectiveness of sorafenib, including the alteration of DCP.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common primary hepatic cancers worldwide and can be treated by liver transplantation, hepatic resection, and percutaneous ablation therapy [1]. However, HCC frequently recurs after curative treatment [2–4], and the prognosis of patients with advanced HCC remains gloomy. The effectiveness of hepatic arterial chemotherapy, radiotherapy, and systemic chemotherapy is limited [2, 3, 5]. Therefore, evidence-based development of molecular-targeted agents for advanced HCC, similar to sorafenib in patients with renal cell carcinoma (RCC), is awaited.

Sorafenib (Nexavar, Bayer HealthCare Pharmaceuticals) is an oral multi-kinase inhibitor that blocks tumor growth and cell proliferation by targeting Raf kinase, vascular endothelial growth factor (VEGF) 2, VEGF 3, and platelet-derived growth factor receptor beta. Recently, two phase 3, randomized, double-blind, placebo-controlled trials showed that sorafenib improves overall survival in patients with advanced HCC [6, 7]. Sorafenib has thus opened a new era for the treatment of advanced HCC. However, most patients who responded to sorafenib had stable disease (SD), and no patient had a complete response (CR) in either study. These results suggested that sorafenib prolongs survival mainly by inducing cancer dormancy, resulting in SD.

We report 2 cases of advanced HCC that rapidly regressed despite treatment with sorafenib for only 1 or 2 weeks. The withdrawal of sorafenib was necessitated by hepatic failure as an adverse event in both patients. In addition, early elevation of des-gamma-carboxy prothrombin (DCP) after the cessation of sorafenib was observed in both patients. These findings suggest that sorafenib has a strong anti-tumor effect even after short-term treatment, and early elevation of DCP might be a predictor of a good outcome. To the best of our knowledge, this is the first case report to document rapid dramatic regression of HCC by sorafenib, accompanied by an early elevation of DCP.

Case Reports

Case 1

An 84-year-old man was admitted to Kitasato University East Hospital (Sagamihara, Japan) because of a single small HCC in June 2005. The patient received radiofrequency ablation (RFA) to treat an initial HCC 2.7 cm in diameter at that time. Well-to-moderately differentiated HCC was diagnosed on percutaneous needle biopsy. Subsequently, 8 sessions of treatment (7 sessions of transarterial chemoembolization (TACE) and 1 of RFA) were performed to treat recurrent lesions. Despite aggressive treatment, an enhanced computed tomographic (CT) scan confirmed multiple sites of recurrence in the liver on January 6, 2010 (**fig. 1**a). The underlying hepatic disease was compensated liver cirrhosis (LC) of Child-Pugh class A due to hepatitis C virus (HCV). The Eastern Cooperative Oncology Group (ECOG) performance status was 0. The DCP level had increased to 966 mAU/ml (normal range <40), while the alpha-fetoprotein (AFP) level was 9.7 mg/dl and within the normal range (<10), and the lectin-bound AFP level was below the detection limit. Sorafenib 800 mg per day was started on an outpatient basis on February 2, 2010. However, general fatigue, appetite loss, and jaundice (total bilirubin 3.2 mg/dl; normal range 0.2–1.0) developed after 1 week of treatment. We diagnosed grade 2 hepatic failure as an adverse event of sorafenib according to the Common Terminology Criteria for Adverse Events version 4.0. We stopped sorafenib without delay. One month after the discontinuation of sorafenib, the patient's clinical symptoms and hepatic function improved completely. On April 26, 2009, 6 weeks after the discontinuation of sorafenib, enhanced CT images showed the disappearance of nearly all viable lesions. After 8 weeks, a partial response (PR) was diagnosed on CT images according to the modified Response Evaluation Criteria in Solid Tumors Guidelines for hepatocellular carcinoma (mRECIST criteria) [8] (fig. 1b). Interestingly, the DCP level rapidly increased to 3,050 mAU/ml after 1 week of sorafenib administration and fell to the normal range within 6 weeks

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after the cessation of sorafenib (fig. 1c). The patient remains well, still shows a PR without treatment for HCC, and continues to be followed up on an outpatient basis.

Case 2

A 58-year-old man, who was a carpenter, was admitted to our hospital because of recurrent HCC in September 2009. A CT scan showed multiple nodules extending to both lobes of the liver. In 2003, the patient had received RFA to treat an initial HCC 3.5 cm in diameter. Well-differentiated HCC was diagnosed on percutaneous needle biopsy. Subsequently, 2 sessions each of RFA and TACE were performed to treat recurrence. However, enhanced CT confirmed multiple sites of recurrence in both lobes of the liver on August 27, 2009 (**fig. 2**a). The underlying hepatic disease was compensated LC of Child-Pugh class A due to HCV. The ECOG performance status was 0. The DCP level was 14 mAU/ml, while the AFP and lectin-bound AFP levels were 20.5 mg/dl and 38.2% (normal range <10), respectively. Sorafenib 800 mg per day was started on an outpatient basis on September 18, 2009. However, flapping tremor, mild altered consciousness with confusion, and hyperammonemia (230 μg/dl; normal range 30–80) developed after 1 week of treatment. Hepatic encephalopathy was diagnosed as a grade 3 drug-related adverse event because there was no evidence of gastrointestinal hemorrhage or sepsis. The patient's symptoms promptly improved after intravenous infusion of branched-chain amino acids. The dose of sorafenib was reduced to 400 mg per day. After receiving the lower dose for 1 week, the patient stopped taking sorafenib on his own initiative because the drug might interfere with his carpentry work. He finally received sorafenib for only 2 weeks. On November 16, 2009, approximately 6 weeks after the discontinuation of sorafenib, enhanced CT images showed the disappearance of nearly all viable lesions (fig. 2b). The therapeutic effect was diagnosed as a PR on CT images obtained every 8 weeks, and the patient was followed up without treatment for HCC. Interestingly, similar to case 1, the DCP level increased to 116 mAU/ml, while the lectin-bound AFP and DCP levels remained flat as compared with the values before sorafenib treatment (fig. 2c). The patient remains well and continues to be followed up on an outpatient basis.

Discussion

The present cases showed rapid and dramatic regression of disease with early elevation of DCP, despite only 1 or 2 weeks' treatment with sorafenib. A CR of advanced HCC is very rare, and only one case report has been documented [9]. However, to the best of our knowledge, rapid regression of advanced HCC with early elevation of DCP after short-term treatment has not been reported previously. The mechanism underlying the rapid regression of disease after short-term treatment with sorafenib is unclear. Phosphorylated extracellular signal-regulated kinase, which is a key downstream component of the Raf/mitogen-activated protein kinase kinase/extracellular signal-regulated kinase signaling pathway, is considered a potential biomarker predictive of sensitivity to sorafenib in patients with HCC [10, 11]. In RCC, sorafenib is effective against RCC that expresses VEGF [12]. Therefore, these factors might be associated with the rapid regression of HCC by sorafenib. Further analyses are required to better define factors underlying sensitivity to sorafenib treatment.

Both of our patients showed temporary elevation of DCP, with no elevation of AFP or lectin-bound AFP. Although elevation of DCP is generally considered an indicator of HCC progression, increased production of DCP by tumor cells was observed in HCC cell lines exposed to a hypoxic environment [13]. This finding suggests that sorafenib-induced suppression of angiogenesis may have caused tumor necrosis via hypoxia in tumor tissues. Therefore, our findings suggest that early elevation of DCP during sorafenib treatment might be a predictor of tumor regression and a good response to sorafenib in contrast to other treatments.

In conclusion, sorafenib-induced rapid regression of advanced HCC even after short-term treatment and the initial response of HCC were identical in both patients. Since

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early elevation of DCP accompanied the PR to sorafenib in both patients, DCP might be a predictive biomarker of anti-tumor effectiveness.

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Both patients gave their written informed consent for the publication of this article.

Fig. 1. Disease response to sorafenib (case 1). Contrast-enhanced CT scans and clinical course are shown. **a** Recurrent multiple HCC was observed before treatment. **b** Multiple HCC had disappeared, except for vestiges of Lipidol (iodized oil) from previous CT scans (6 weeks after the discontinuation of sorafenib). **c** Temporary rapid elevation of the DCP level was observed even after only 1 week of sorafenib, while the AFP value remained within the normal range throughout the observation period.

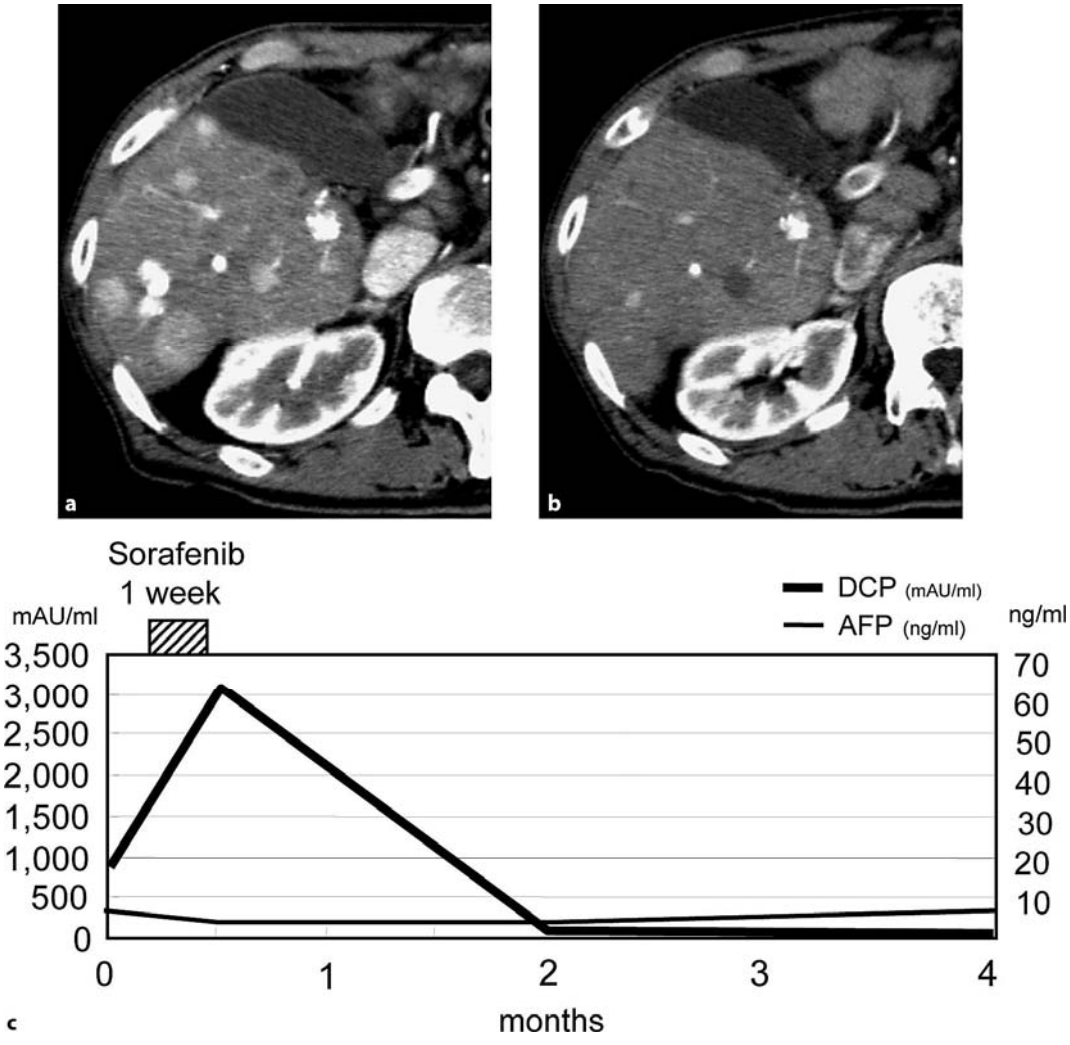

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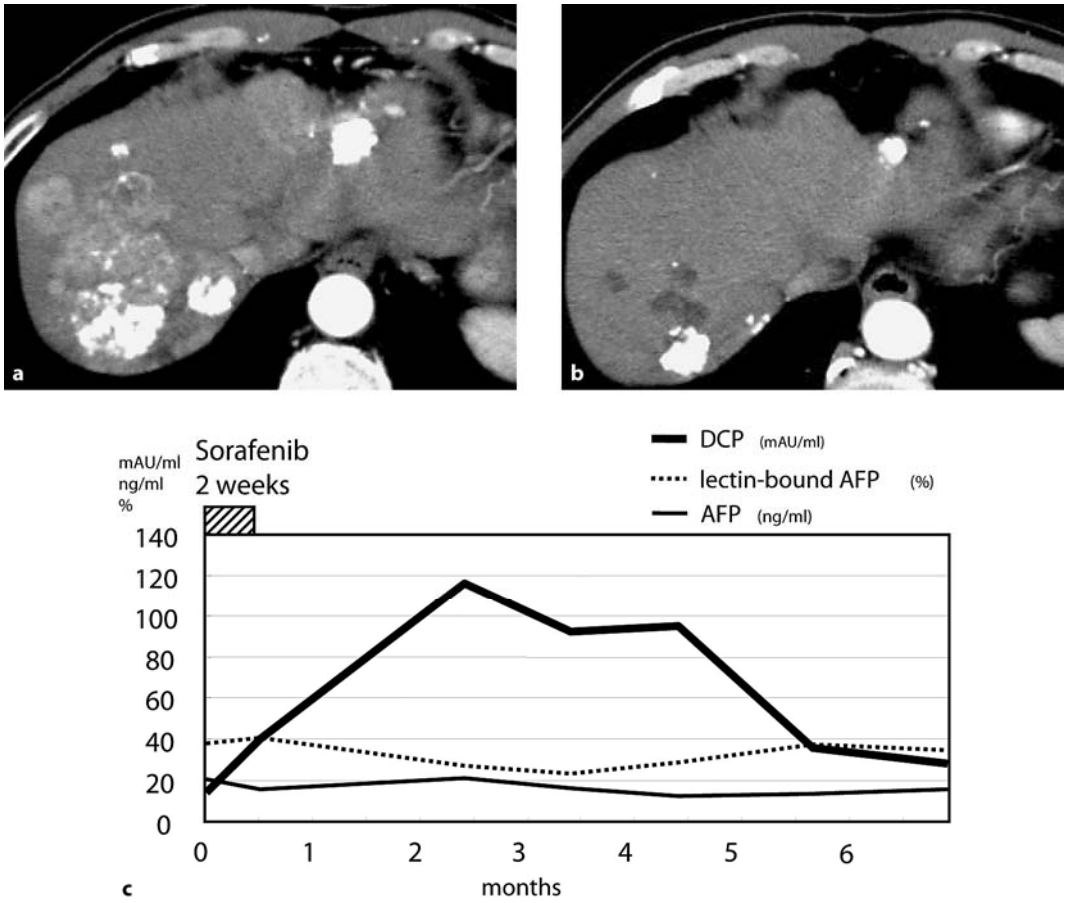
Fig. 2. Disease response to sorafenib (case 2). Contrast-enhanced CT scans and clinical course are shown. **a** Recurrent multiple HCC of the liver was observed before treatment. **b** Multiple HCC had disappeared, except for vestiges of Lipidol (iodized oil) from previous CT scans (6 weeks after the discontinuation of sorafenib). **c** A temporary gentle elevation of the DCP level was observed after treatment with sorafenib, while the AFP and lectin-bound AFP values remained nearly flat throughout the observation period.



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