

## 우심방 전체를 침범한 진행성 간세포암종에서의 소라페닙 치료

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## Sorafenib Treatment in Advanced Hepatocellular Carcinoma with Tumor Thrombus Nearly Occupying the Entire Right Atrium

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Advanced hepatocellular carcinoma (HCC) with tumor thrombus extending through the hepatic veins, inferior vena cava, and right atrium (RA) is very rare. However, whether active treatments such as radiation, transcatheter arterial chemoembolization, and sorafenib in advanced HCC with RA involvement prolong survival is uncertain. We present a rare case of advanced HCC with tumor thrombus nearly occupying the entire RA that was treated with sorafenib. The patient received 400 mg sorafenib twice daily. However, her liver enzyme levels continued to increase and abdominal computed tomography showed an increase in the tumor size in the liver and RA. In the present case, active treatment with sorafenib was ineffective; thus, palliative care may be more beneficial in advanced HCC with extensive RA involvement. (*J Liver Cancer* 2018;18:142-145)

**Keywords:** Sorafenib; Thrombosis; Hepatocellular carcinoma ; Right atrium

### INTRODUCTION

Hepatocellular carcinoma (HCC) is the seventh-most common carcinoma worldwide and the third-most common cause of cancer-related mortality.<sup>1</sup> HCC often metastasizes to the lymph nodes, bones, and lungs. Although rare, intracardiac involvement is possible. The prognosis of patients with cardiac involvement of HCC is very poor.<sup>2</sup> The effectiveness

of active treatments such as radiation, transcatheter arterial chemoembolization (TACE), and sorafenib in prolonging survival in advanced HCC with heart involvement is uncertain.<sup>3</sup> Herein, we report a very rare case of sorafenib treatment in a patient with advanced stages of HCC with a tumor thrombus occupying most of the right atrium (RA).

### CASE REPORT

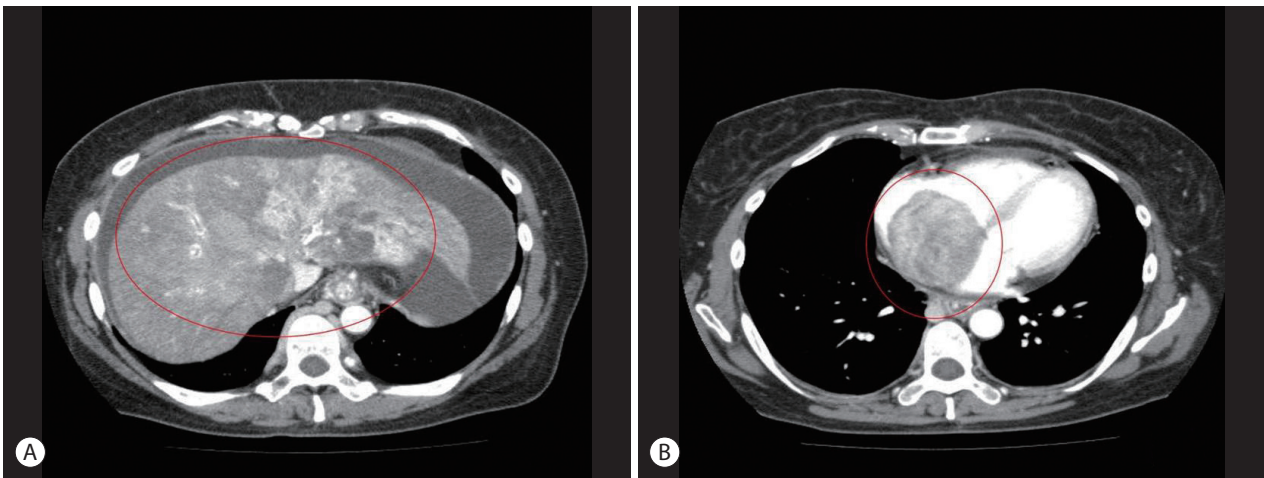
A 60-year-old woman, who was a hepatitis B virus carrier, presented to the hospital with a chief complaint of fatigue and dyspnea. Abdominal computed tomography (CT) scan revealed a large HCC with a 5 × 4 cm tumor thrombus extending through the hepatic vein (HV) and inferior vena

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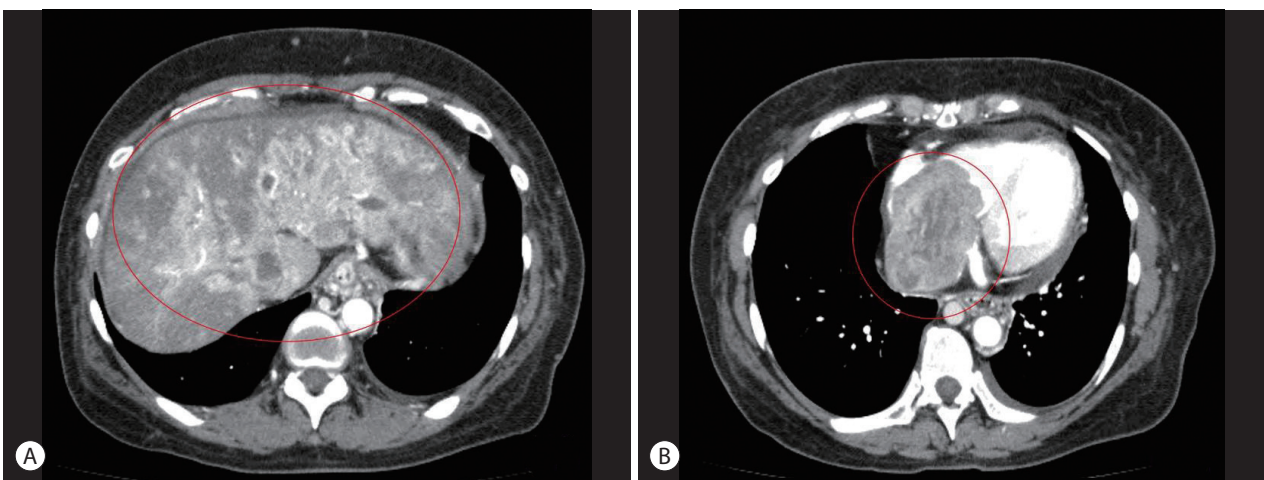
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cava (IVC) and into the RA (Fig. 1). She appeared chronically ill, with a blood pressure of 110/60 mmHg, a heart rate of 84 beats/min, a respiratory rate of 20 breaths/min, and a body temperature of 36.5°C. Blood tests showed a white blood cell count of 6,720/mm<sup>3</sup>, hemoglobin level of 14.0 g/dL, platelet count of 171,000/ $\mu$ L, aspartate aminotransferase (AST) concentration of 206 IU/L, alanine aminotransferase (ALT) concentration of 152 IU/L, total protein level of 6.0 g/dL, total albumin level of 3.3 g/dL, prothrombin time of 66%, and total bilirubin concentration of 1.2 mg/dL. Her alpha-fetoprotein level was significantly elevated to 3,709 ng/

mL. According to the Barcelona Clinic Liver Cancer staging system, the patient had advanced staged HCC associated with Child-Pugh Class A cirrhosis and Eastern Cooperative Oncology Group (ECOG) performance status of 1. The patient was treated with sorafenib 400 mg twice daily beginning on the twenty-second day of hospital admission. On the twenty-first hospital day, before sorafenib treatment, the laboratory results showed AST concentration of 133 IU/L, ALT concentration of 83 IU/L, and total bilirubin concentration of 0.7 mg/dL. However, after sorafenib administration, the liver enzyme levels gradually increased. On the twenty-sixth



**Figure 1.** Contrast-enhanced abdominal computed tomography scan findings. The CT showed multiple diffuse type HCC (red circle) (A), and a 5 × 4 cm sized tumor thrombus in the right atrium (red circle) (B). CT, computed tomography; HCC, hepatocellular carcinoma.



**Figure 2.** Follow-up abdominal computed tomography scan findings. It showed HCC aggravation (red circle) (A), and increased tumor thrombus to 7.4 × 6 cm in the right atrium (red circle) (B). HCC, hepatocellular carcinoma.

hospital day, the laboratory results showed AST concentration of 367 IU/L, ALT concentration of 200 IU/L, and total bilirubin concentration of 2.6 mg/dL. As a result, on the twenty-sixth hospital day, the dose of sorafenib was reduced to 400 mg once daily. Although the dose of sorafenib was reduced, the liver enzyme levels continued to worsen and on the twenty-eighth hospital day, the laboratory results showed AST concentration of 916 IU/L, ALT concentration of 489 IU/L, total bilirubin concentration of 2.4 mg/dL. On the twenty-seventh hospital day, a follow-up abdominal CT showed an increase in the size of the tumor occupying the RA (7.4 × 6 cm) (Fig. 2). Subsequently, on the 28th hospital day, sorafenib was discontinued on day six of treatment. The patient was then treated conservatively with palliative care. However, her hepatic function continued to decline while she gradually developed dyspnea. The patient died on the 40th day of admission.

## DISCUSSION

Over 650,000 people die of HCC worldwide each year and at least two-thirds of these deaths are in East Asia.<sup>4</sup> The incidence of HCC is increasing in the United States and Europe and it is the third-highest cause of cancer-related deaths globally, following lung and stomach cancer.<sup>5</sup>

HCC often metastasizes to the lymph nodes, bones, and lungs, and also has a tendency for vascular invasion.<sup>2</sup> Intra-cardiac metastases can occur either as an isolated metastasis or by direct extension of the tumor with an associated thrombus. As the tumor penetrates the vascular structures, the invading cells stimulate thrombus growth, providing a favorable environment for the rapid proliferation of tumor cells.<sup>2</sup> HCC can invade vascular structures such as the portal vein and the hepatic vein. The tumor thrombi may rarely extend into the IVC. However, cases of tumor thrombus extending into the RA in HCC patients are very rare.<sup>6</sup> When HCC extends into the heart, the prognosis is very poor.<sup>3</sup> The mean survival in HCC patients with RA extension is one to four months, regardless of treatment.<sup>6,7</sup> The treatment options include surgical excision, systemic chemotherapy, TACE, radiation, and molecular targeted therapy like

sorafenib.<sup>2</sup>

Chun et al.<sup>8</sup> retrospectively analyzed 50 patients with HCC involving the IVC and heart. The control group (n=30) received best supportive care (BSC) and the other group (n=32) received active treatment. The treatment methods in the active treatment group included systemic chemotherapy using 5-fluorouracil with or without cisplatin (n=10), TACE (n=8), intra-arterial chemotherapy (n=3), concurrent chemoradiation therapy (n=3), radiation (n=2), surgery (n=1), and combinations of the above (n=5). Active treatments such as radiation, systemic chemotherapy, and TACE, compared with BSC, provided a survival benefit in patients with HCC that extended into the IVC and heart (median 4.0 vs. 2.0 months,  $P=0.003$ ). These results indicated that active treatment in carefully selected patients might provide a survival benefit.<sup>8</sup> Lin et al.<sup>9</sup> retrospectively analyzed eight HCC patients with cardiac metastasis who were treated by surgical excision. They reported that surgical treatment may prolong the survival of HCC patients with cardiac involvement. Rim et al.<sup>10</sup> reported that external beam radiation therapy (EBRT) is a safe option for HCC with IVC and RA involvement. We initially considered surgical resection or EBRT for this patient. However, we decided to treat with sorafenib after a full explanation and discussion with the patient due to the high operative risk and concern for the spread of tumor emboli after radiotherapy.

Advanced HCC has been treated with sorafenib, an oral chemotherapeutic agent that targets several tyrosine kinase-dependent molecular pathways such as vascular endothelial growth factor and platelet-derived growth factor-beta. These pathways allow for the proliferation of HCC. Therefore, sorafenib has been associated with reduced angiogenesis and increased apoptosis of tumor cells in HCC.<sup>5</sup> The benefit of sorafenib was consistent in patients with the worst prognosis, such as those with an ECOG performance status of 1 or 2 or with macroscopic vascular invasion or extrahepatic spread.<sup>5</sup>

Jun et al.<sup>3</sup> retrospectively analyzed a total of 665 patients with HCC. The patients were divided into two groups, 33 patients with HCC extending into the RA and 632 HCC patients, during the same period. The patients with HCC extending into the RA were subdivided into a shorter (<2

months) and longer ( $\geq 2$  months) survival groups. In their study, the prevalence of HCC extending to the RA was 4.96%. Union for International Cancer Control stage higher than IVa, HV invasion, concomitant IVC and portal vein invasion, and multinodular tumors were risk factors for HCC extending to the RA. Active treatments such as radiation, TACE, sorafenib, and combined modalities ( $P=0.024$ ; odds ratio, 0.054) were associated with a better prognosis in patients with HCC extending into the RA. These findings suggest that active treatments may prolong survival in patients with HCC extending into the RA. However, in the present case, sorafenib treatment did not prolong survival due to hepatic failure.

Active treatment with surgery, TACE, radiation, and sorafenib may be considered a treatment option in carefully selected patients with advanced HCC with IVC and RA with good performance status and liver function. Further studies are needed to develop the best treatment strategies for these patients.

### Conflicts of Interest

The authors have no conflicts to disclose.

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