

## Case Research

# Long-term survival of patients with hepatocellular carcinoma with inferior vena cava tumor thrombus treated with sorafenib combined with transarterial chemoembolization: report of two cases and literature review

Heng-Jun Gao, Li Xu, Yao-Jun Zhang and Min-Shan Chen

## Abstract

The prognosis of hepatocellular carcinoma (HCC) with tumor thrombus formation in the main vasculature is extremely poor. Sorafenib combined with transarterial chemoembolization is a novel treatment approach for advanced HCC. In this study, we report two HCC patients with inferior vena cava tumor thrombus who underwent the combination treatment. The overall survival times for these two patients were 44 months and 35 months, respectively. Our report suggests that sorafenib combined with transarterial chemoembolization may be a viable choice for patients with advanced HCC even with inferior vena cava tumor thrombus. Further studies are required to verify the efficacy and safety of this combination therapy for patients with advanced HCC with inferior vena cava tumor thrombus.

**Key words** Hepatocellular carcinoma, sorafenib, transarterial chemoembolization, inferior vena cava, tumor thrombus

Hepatocellular carcinoma (HCC), one of the most common malignant tumors in the world, is increasing in incidence<sup>[1,2]</sup> and is a leading cause of death among patients with liver cirrhosis<sup>[3]</sup>. In spite of the surveillance programs for HCC, most patients are diagnosed at the intermediate or advanced stages for which there is no curative therapy, resulting in a dismal prognosis. The prognosis is particularly poor for patients with HCC with tumor thrombus in the main vasculature, such as the portal vein, hepatic vein, and even inferior vena cava; the median survival time of untreated patients is only 9 to 10 weeks<sup>[4]</sup>.

According to the Barcelona Clinic Liver Cancer (BCLC) staging system, sorafenib is the standard treatment for HCC with vascular invasion and/or distant metastasis (BCLC stage C), whereas transarterial chemoembolization (TACE) is recommended for HCC of BCLC stage B. Recently, TACE has been reported to have similar or even better safety and efficacy in some advanced HCC cases

compared with sorafenib<sup>[5]</sup>, including HCC with main vessel tumor thrombus. However, both sorafenib and TACE have only modest survival benefit when used alone, highlighting the urgent need for a novel treatment approach<sup>[6]</sup>.

TACE has a potential stimulatory effect on angiogenesis. This observed effect is related to up-regulation of local angiogenic factors, which in turn promote tumor growth, increasing the risk of metastases and potentially worsening outcome<sup>[7]</sup>. In contrast, sorafenib down-regulates angiogenesis and induces apoptosis in cancer cells<sup>[8]</sup>. Theoretically, the combination of TACE and sorafenib has the potential to be more efficacious than either approach alone. Here we present 2 patients with HCC with inferior vena cava tumor thrombus who underwent TACE combined with sorafenib. We also provide a review of the relevant literature.

## Cases Report

### Case 1

The patient was a 33-year-old man who presented with abdominal distension and edema of the lower limbs for approximately 20 days. Blood tests were negative for viral hepatitis and showed normal liver function, prothrombin time, and significantly increased alpha-fetoprotein (AFP) value (17,201 ng/mL). Doppler ultrasonography and enhanced computed tomography (CT) with contrast showed a

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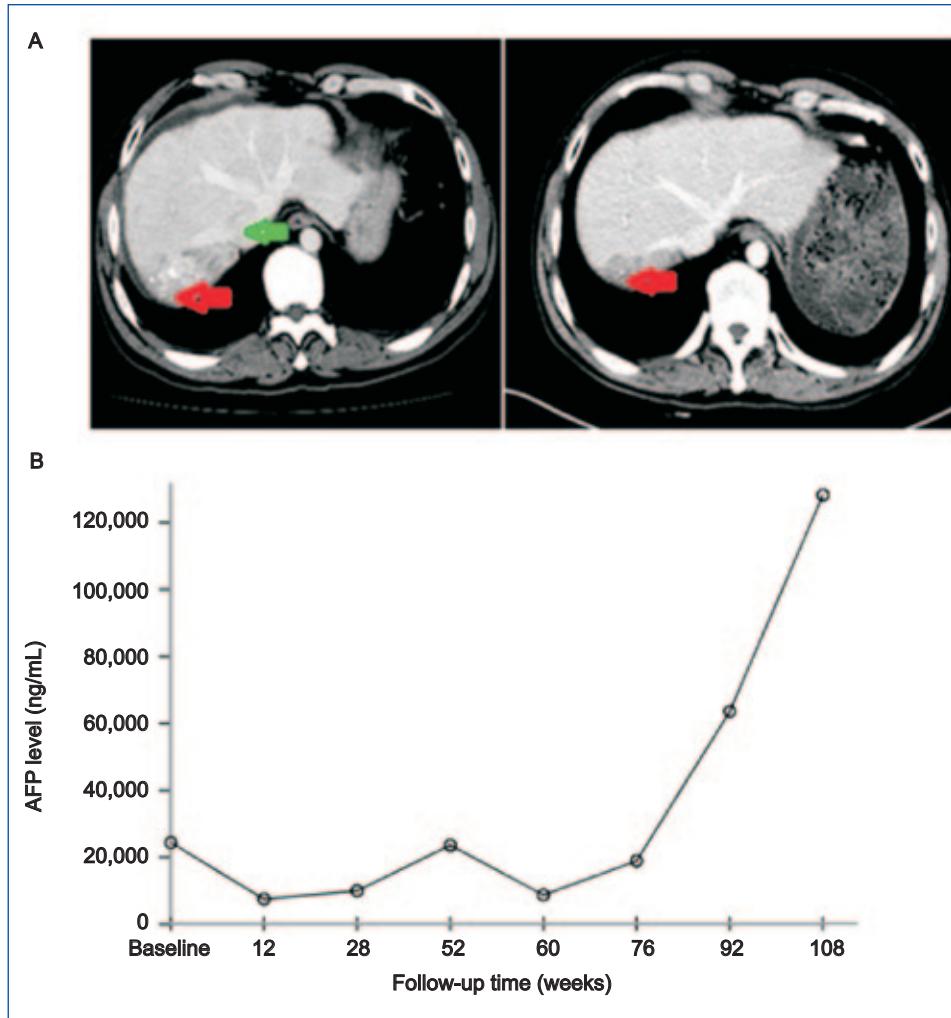
**doi:** 10.5732/cjcc.013.10133

tumor lesion 6.5 cm in diameter located in segments VI and VII with multiple intrahepatic metastases. The tumor had direct invasion into the inferior vena cava and presented with a tumor thrombus 2.0 cm in length. Slight ascites was also present. Needle biopsy confirmed the histologic diagnosis of HCC (pathologic grade III). The Child-Pugh score was 6 (class A). The Eastern Cooperative Oncology Group performance status (ECOG PS) was 1. The disease stage was determined to be T3bN0M1 according to the American Joint Committee on Cancer (AJCC) staging system and advanced stage (stage C) according to the BCLC staging system.

TACE was first performed to control the primary tumor, using 50 mg of epirubicin (Pharmorubicin, Pfizer, Wuxi, China) mixed with 10 mL of Lipiodol (Lipiodol Ultra-Fluide; Andre' Guerbet Laboratories, Aulnay-Sous-Bois, France) and absorbable gelatin sponge particles (Gelfoam; Hangzhou alc Ltd, China). Subsequently, the patient was treated with 400 mg of sorafenib twice daily. Tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 and modified RECIST (m-RECIST) every 2 months. The patient's best response was stable disease (SD) by RECIST and partial response (PR) by m-RECIST, respectively (**Figure 1A**).

Progressive disease (PD) was found in the 14th month after the initial treatment. Then another TACE with the same formula was performed to enhance local control of the intrahepatic lesions, with sorafenib continued. Radiologic SD was once again achieved and lasted for another 18 months, even though the serum AFP level continued to rise during follow-up (**Figure 1B**). In the 33rd month after the initial treatment, the intrahepatic lesions had significant progression with liver function deteriorating to Child-Pugh class C. The inferior vena cava tumor thrombus remained stable until the last follow-up. Sorafenib was discontinued due to severely impaired liver function at that time, and the best supportive care was given as the only treatment. Finally, the patient died from progressive liver disease 44 months after the initial treatment.

The primary TACE-related adverse event was grade 3 post-embolization syndrome (transient fever, abdominal pain, and elevated transaminases). The sorafenib-related adverse events consisted of grade 3 hand-foot skin reaction, grade 2 alopecia, tinnitus, and diarrhea. Sorafenib had been interrupted for no more than 7 days due to grade 3 hand-foot skin reaction during the first 3 months of treatment. The adverse events of sorafenib declined and were well



**Figure 1.** The computed tomography (CT) images before and after treatment of sorafenib and serum alpha-fetoprotein (AFP) level dynamic curve of case 1. A, the image on the left is CT scan after transarterial chemoembolization (TACE) without starting of sorafenib, showing tumor (red arrow) with accompanying invasion of the inferior vena cava (green arrow). The image on the right is CT scan after 20 months of sorafenib treatment. Range of the primary lesions becomes clear and smaller, with the shrinkage of the inferior vena cava tumor embolus after the sorafenib treatment. B, serum AFP level of case 1 during treatment (tested by ELISA). The descended part of curve shows significant tumor control after TACE and sorafenib treatment. The disease remained controlled for nearly 52 weeks with maintenance treatment of sorafenib alone. After the second TACE in the 56th week and the continuous sorafenib, AFP dropped again and radiologic stable disease (SD) maintained for another 18 months. However, the serum AFP level began to rise from the 76th week.

tolerated after 3 months.

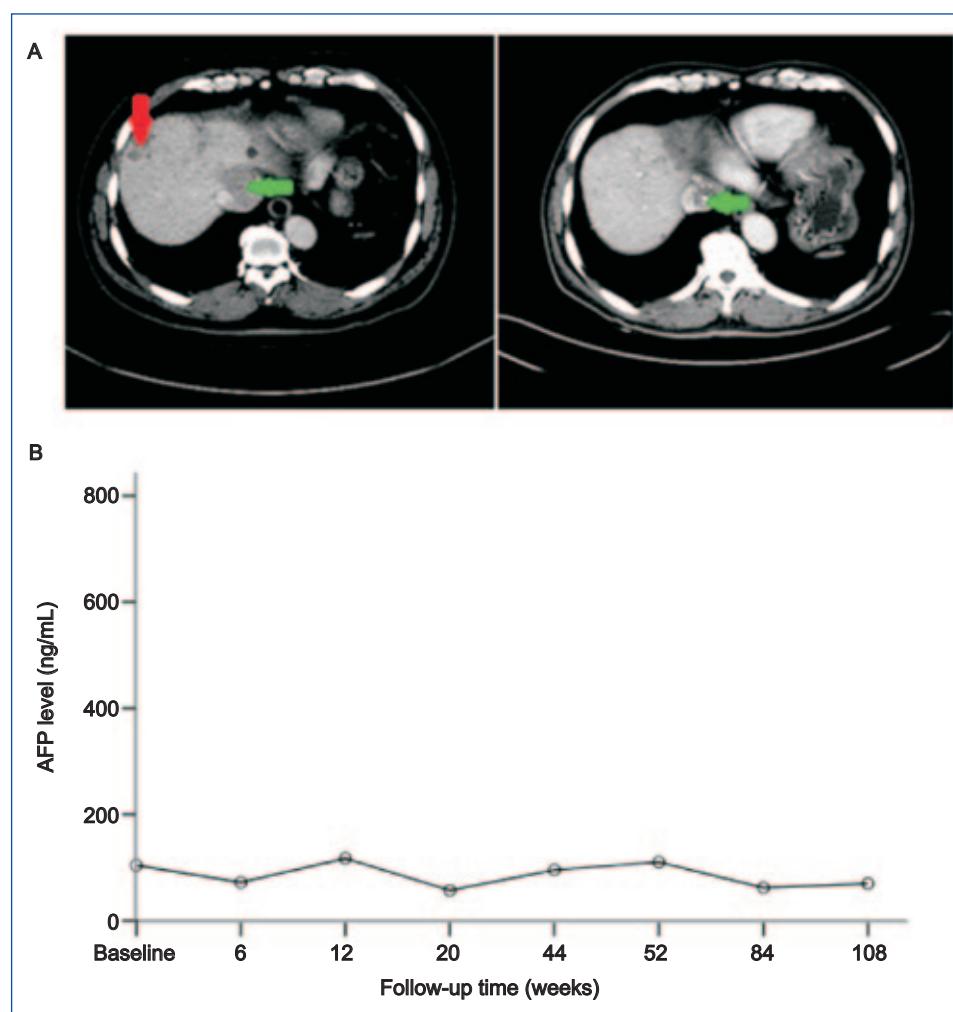
## Case 2

The patient was a 60-year-old man who presented asymptomatic when hepatic lesions were found on regular ultrasound surveillance due to hepatitis B virus infection. Both spiral CT and magnetic resonance imaging (MRI) with contrast were performed to confirm the clinical diagnosis of HCC. Radiologic examination revealed multiple tumors with maximum 5.0 cm in diameter located in segments IV and VIII with direct invasion of the middle hepatic veins, and tumor embolus extending to the inferior vena cava for 4 cm. Other investigations showed compensated liver function and mildly increased AFP (73.83 ng/mL). The Child-Pugh score was 5 (class A) and the ECOG PS was 0. The disease was evaluated as T3bN0M1 according to the AJCC staging system and advanced stage (stage C) HCC in the BCLC staging system.

TACE was carried out as the initial treatment with the same formula as Case 1. Sorafenib (400 mg twice daily) was given orally 5 days later. TACE was repeated twice monthly to further ensure tumor

destruction. Sorafenib was interrupted for 3 days during TACE and then continued. The patient was followed up with enhanced spiral CT scan and AFP test every 2 months. Intrahepatic lesions responded satisfactorily to treatment with the inferior vena cava tumor embolus remaining stable (SD according to RECIST criteria and PR by m-RECIST, respectively; **Figure 2A**). AFP level had no significant elevated trend during follow-up (13.25–73.85 ng/mL, **Figure 2B**). At the last follow-up in April 2013, the patient had no evidence of progressive disease and had survived for 35 months after the initial treatment with a good performance status (ECOG PS 1). Sorafenib was still continued at a dose of 400 mg twice daily.

Grade 2 post-embolization syndromes occurred in the first week post-TACE but were relieved after symptomatic treatment. Sorafenib-related adverse events consisted of grade 1 tinnitus and diarrhea. Grade 2 hypertension occurred after 2 months of sorafenib therapy and was thought to be sorafenib-related. Valsartan and nifedipine were prescribed to control hypertension. Entecavir was also prescribed for hepatitis B. No adverse event-related interruption or discontinuation of sorafenib occurred.



**Figure 2.** The CT images before and after treatment and serum AFP level dynamic curve of case 2. A, the image on the left is CT scan before treatment. Multiple lesions (red arrow) are shown in the liver with tumor thrombus invading to the inferior vena cava (green arrow). The image on the right is CT scan after 29 months of treatment. Both intrahepatic lesions and the inferior vena cava tumor embolus presented obvious response after the combination therapy of TACE and sorafenib. B, serum AFP level of case 2 during treatment. With a relatively low value of AFP (73.83 ng/mL) at the baseline, the curve showed no significant increase and decrease, and remained stable during treatment. The combination therapy of TACE and sorafenib got a satisfactory effect and lasted for over 2 years in this patient.

## Discussion

Vascular invasion is an important prognostic factor for patients with HCC<sup>[6]</sup>. Prognosis is markedly worse for patients with inferior vena cava tumor thrombus compared with those with thrombus formation in other branch vessels<sup>[9,10]</sup>. Earlier observations revealed that the median survival time of untreated patients was only 9 to 10 weeks from the time of diagnosis<sup>[11-14]</sup>. Sorafenib is the recommended standard treatment for patients with advanced HCC (including patients with main vessel invasion and extrahepatic metastasis). However, other therapies have been reported in previous studies to improve the survival of these patients<sup>[15-17]</sup> (**Table 1**). For example, surgical resection of primary tumor en bloc with tumor thrombus, TACE, and radiotherapy may prolong survival<sup>[12,15-19]</sup>. Traditionally, TACE has not been considered suitable for HCC patients with major vascular invasion due to the high risk of hepatic infarction. However, Lee *et al.*<sup>[20]</sup> recently reported that TACE is a safe treatment option for patients with HCC and portal vein trunk obstruction, but only in those with good liver functional reserve and sufficient collateral circulation around the portal trunk. Luo *et al.*<sup>[21]</sup> indicated that treatment with TACE can improve long-term survival for patients with portal vein tumor thrombus. Moreover, the combination of TACE and three-dimensional conformal radiotherapy was more effective in the control of inferior vena cava tumor thrombus associated with HCC and improved patient survival compared with TACE alone<sup>[20]</sup>. Surgical resection has also been suggested as a treatment choice due to the increased survival of some patients with major vessel thrombus. Pawlik *et al.*<sup>[9]</sup> reported that the median survival after hepatic resection for HCC with major vascular invasion exceeded the survival of patients not treated surgically, particularly in patients with little or no liver fibrosis. Wang *et al.*<sup>[15]</sup> showed that surgery for HCC with inferior vena cava/right atrium thrombus could significantly improve patient survival compared with TACE or symptomatic treatment. Due to the severe complications and mortality associated with surgical resection, surgery may not be indicated for all HCC patients and must be carefully considered.

Sorafenib, an inhibitor of cancer cell proliferation and tumor angiogenesis, has been approved for treatment of advanced HCC based on two randomized, placebo-controlled trials<sup>[22,23]</sup>. Although

sorafenib therapy results in statistically significant improvements in overall survival, time-to-tumor progression, and disease control rate, these improvements are only clinically modest. As a result, sorafenib combined with other treatments became a potentially ideal strategy for treating advanced HCC. Several prospective trials are already started worldwide aim to confirm the efficacy of combination treatment.

Theoretically, TACE creates a hypoxic environment for remnant tumor cells<sup>[7]</sup>, stimulating surviving cells to express vascular endothelial growth factor (VEGF), which may lead to neovascularization and reestablishment of the tumor's blood supply<sup>[24]</sup>. Thus, the addition of an antiangiogenesis agent, sorafenib—which inhibits VEGF receptors, seems to be a good choice for combination with TACE. VEGF or VEGFR may also be a useful biomarker with which to predict the efficacy of combination therapy in clinical practice. However, we did not validate the level of VEGF and VEGFR for the two patients described above.

Besides, sorafenib combined with cytotoxic drug shows an impossible synergism as that sorafenib inhibits the Ras/Raf/MEK/ERK pathway, which will prevent activation of the multidrug resistance pathway that mainly induce the failure of chemotherapy in HCC<sup>[25]</sup>. A randomized controlled trial verified that sorafenib plus doxorubicin resulted in longer median time-to-progression, overall survival, and progression-free survival<sup>[26]</sup>. It gives the potential that the combined sorafenib and transarterial chemotherapy can enhance the efficacy of each therapy alone to some extent.

In the two patients with HCC with inferior vena cava tumor thrombus described here, the sorafenib and TACE combination achieved surprising outcomes and significantly prolonged the patients' survival. From that, we propose that several factors associated with the combination of sorafenib and TACE need to be considered. The first is how we determine the protocol by which to administer sorafenib treatment and TACE therapy. There are three theoretical models of combination treatment: the sequential approach, where sorafenib is initiated as an adjuvant post-TACE; the interrupted approach, where sorafenib therapy is paused for 3–5 days, during which TACE is performed to avoid possible adverse events; and the continuous approach, where the patient is administered sorafenib without interruption, in addition to TACE treatment. Strelbel *et al.*<sup>[27]</sup>

**Table 1.** Literature review of the treatment of HCC patients with inferior vena cava tumor thrombus

Reference	Number of patients	Treatment modality	Primary complications	Median survival (months)
Wang <i>et al.</i> <sup>[15]</sup>	25	Surgery	Bile leakage, ascites, etc.	19.0
	20	TACE	Not available	4.5
Jung <i>et al.</i> <sup>[16]</sup>	5	Surgery	Postoperative bleeding, etc.	33.1
Chern <i>et al.</i> <sup>[17]</sup>	26	TACE	Ascites, etc.	4.2
Zeng <i>et al.</i> <sup>[12]</sup>	44	Radiation therapy	Radiation-induced hepatic injury	8.0
Koo <i>et al.</i> <sup>[19]</sup>	42	TACE + radiation therapy	Radiation-induced hepatic injury	11.7

HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

suggested that the continuous approach may be more efficacious; however, increased adverse events were also presented. The two patients in our study were treated with the interrupted approach to avoid possible augmentation of adverse events. The related adverse events were slight and well tolerated. There were no serious adverse events, grade 4 drug-related adverse events, or discontinuations due to adverse events. Our cases suggest that the interrupted approach was both well tolerated and effective, and that sorafenib combined with TACE is a good strategy for clinical practice. The second point to consider is sorafenib discontinuation. Traditionally, chemotherapy is discontinued when progressive disease is noted. To date, no second-line therapy has been established for HCC patients after sorafenib failure. As a molecular targeted drug, sorafenib presents a good safety profile and long-lasting effect that confer clinical benefit to patients even after disease progression with radiotherapy. The special "re-SD" occurred in Case 1 and reached another 18 months of stable phase with sorafenib maintenance therapy. Accordingly, we suggest that patients who have achieved disease control may continue sorafenib even after radiologic disease progression, as long as they have good performance status and compensatory liver function. More intensive monitoring of liver function should be performed in those patients for safety reasons. The third point to discuss is how sorafenib efficacy should be evaluated in clinical practice. Personeni *et al.*<sup>[28]</sup> stated that assessment of AFP response may be an alternative to RECIST in evaluation of sorafenib activity in HCC. In some cases, a decrease in AFP concentration implies tumor destruction; however, generally, absolute concentration of AFP cannot be regarded as a biomarker for tumor progression or tumor

regression. In the present report, Cases 1 and 2 both achieved lasting radiologic SD despite increasing AFP levels. AFP response failed to predict the tumor response and survival of these patients. Edeline *et al.*<sup>[29]</sup> compared the sensitivity of m-RECIST with RECIST in patients receiving sorafenib for advanced HCC. They concluded that m-RECIST was more sensitive in predicting survival in HCC patients treated with sorafenib. The m-RECIST assessment is based on measuring the size of intrahepatic lesions as viewed on CT/MRI with arterial contrast. Both cases we reported here had partial response by m-RECIST assessment and achieved rarely long survival. m-RECIST may be helpful in evaluating intrahepatic lesions. Adaptive and detailed criteria need to be established for the assessment of the response of the tumor thrombus.

In conclusion, sorafenib combined with TACE may be a therapeutic choice for patients with advanced HCC with inferior vena cava tumor thrombus who have adequate performance status and liver function. The results of these two cases are encouraging. However, further prospective clinical trials are warranted to explore its benefit on long-term survival of patients with extremely advanced HCC.

## Acknowledgments

We appreciate Prof. Yun-Fei Yuan and Prof. Ming Shi for recommending patients.

Received: 2013-07-19; revised: 2013-10-06;  
accepted: 2013-10-30.

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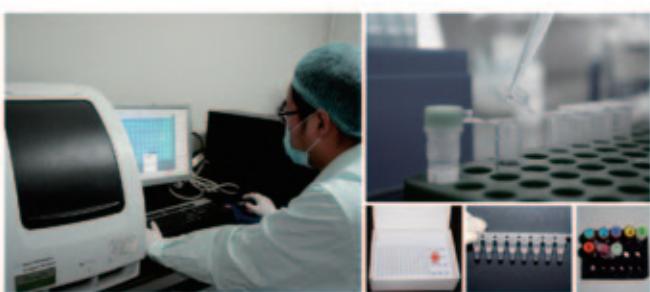


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