Case Report

Deteriorated portal flow may cause liver failure in patients with hepatocellular carcinoma being treated with sorafenib

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Abstract: We encountered two patients with hepatocellular carcinoma (HCC) who showed rapid progression of liver failure during sorafenib treatment. One had portal vein tumor thrombus (PVTT) and the other developed portal vein thrombosis (PVT) during the treatment, and both of them experienced the elevation of serum lactate dehydrogenase (LDH) concentration during the administration of sorafenib. Their clinical courses indicate that the liver failure might have been caused by sorafenib-induced liver hypoxia, being amplified in the circumstances with reduced portal flow. To our best knowledge, all the reported patients who achieved complete remission (CR) during sorafenib monotherapy had a condition that could decrease portal blood flow. We hypothesized that pathogenesis of disease may be similar in HCC patients who achieve CR and those who experience liver failure while on sorafenib. Sorafenib treatment of patients with HCC and deteriorated portal flow may be a double-edged sword.

Keywords: Sorafenib; hepatocellular carcinoma (HCC); liver failure

Submitted Sep 16, 2015. Accepted for publication Sep 30, 2015.
doi: 10.21037/jgo.2015.10.07
View this article at: http://dx.doi.org/10.21037/jgo.2015.10.07

Introduction

Based on two phase III randomized trials showing that sorafenib, a multi-kinase inhibitor, prolonged overall survival in patients with advanced hepatocellular carcinoma (HCC) and Child-Pugh A cirrhosis, sorafenib was approved for the treatment of patients with advanced HCC (1,2). Although none of the patients in those studies developed liver failure during sorafenib treatment, several subsequent studies showed that sorafenib could cause liver failure, especially in patients with poorer Child-Pugh stages (3,4). To date, however, the clinical characteristics and subsequent clinical course of patients who experienced liver failure during treatment with sorafenib have not yet been clarified.

We recently encountered two patients with HCC who showed rapid progression of liver failure during sorafenib treatment. One had portal vein tumor thrombus (PVTT) and the other developed portal vein thrombosis (PVT) during the treatment. Although both PVTT and PVT are regarded as negative prognostic factors for patients with HCC, previous studies have identified several patients with deteriorated portal flow who achieved complete remission (CR) while being treated with sorafenib (5-17). We hypothesized that the pathogenesis of disease may be similar in HCC patients who achieve CR and those who experience liver failure while on sorafenib. A detailed information understanding of their clinical characteristics may contribute to a better understanding of the effects of sorafenib.

Case presentation

Patient 1

A 64-year-old man was admitted to our hospital for general fatigue. He had a more than 10-year history of alcohol abuse and had been diagnosed with alcoholic liver cirrhosis 4 years prior to admission. Contrast-enhanced computed tomography (CT) showed a 10 cm mass with high-low pattern in the right lobe of his liver and a tumor thrombus in the portal right branch extending to the main trunk, but no ascites (*Figure 1*). Based on imaging results,

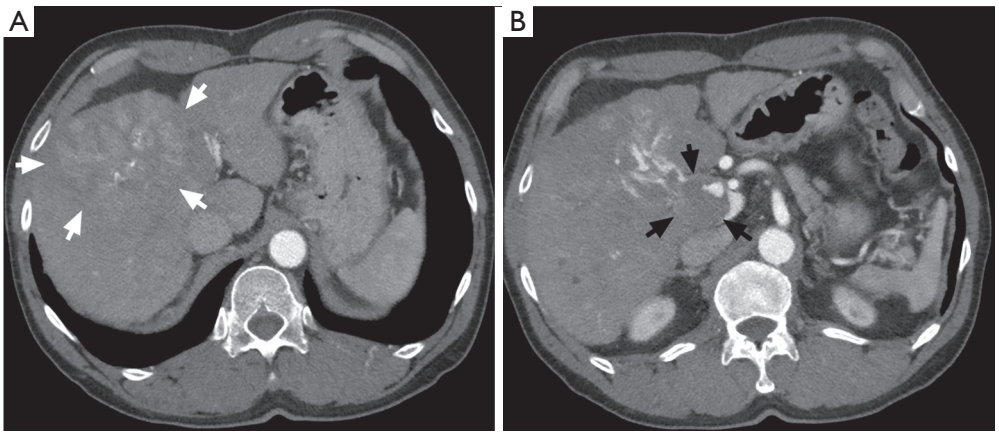

Figure 1 Contrast-enhanced CT image of patient 1. The huge mass in the right lobe with a high-low pattern was consistent with HCC (white arrow). The tumor thrombus in the portal right branch extended to the main trunk (black arrow). CT, computed tomography; HCC, hepatocellular carcinoma.

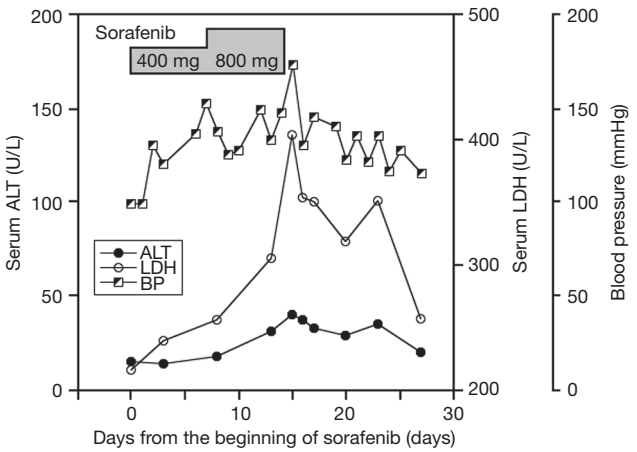

Figure 2 The clinical course of patient 1. At the start of sorafenib treatment, his blood pressure and serum LDH level became elevated. After the dose of sorafenib was increased to 800 mg/day, his LDH level increased. Hepatic encephalopathy, along with markedly increased blood pressure, abruptly appeared on day 14 of sorafenib treatment. ALT, alanine aminotransferase; LDH, lactate dehydrogenase; BP, blood pressure.

the patient was diagnosed with HCC. At admission, he had a total bilirubin concentration of 1.3 mg/mL, an alanine aminotransferase (ALT) concentration of 50 IU/L, a lactate dehydrogenase (LDH) concentration of 200 IU/L, an ammonia concentration of 67 μg/dL, and a prothrombin time international normalized ratio (PT-INR) of 1.10. His liver function was graded as Child-Pugh A. Serum concentrations of HCC tumor markers were markedly elevated, with a des-gamma-carboxy prothrombin concentration (DCP) of 1,171 mAU/mL and an α-fetoprotein concentration of 9,914 ng/mL. Initial treatment consisted of hepatic arterial infusion chemotherapy with 5-fluorouracil and cisplatin for 3 weeks, which resulted in stable disease. Following an interval of 3 weeks, the patient was started on sorafenib 400 mg/day for 7 days. Because the only adverse effect observed was a slight elevation in blood pressure (BP), his sorafenib dose was increased up to 800 mg/day. On the morning of day 14 of sorafenib treatment, the patient abruptly became disoriented, and his systolic BP increased to 180 mmHg (*Figure 2*). He experienced asterixis and his serum ammonia concentration increased to 153 μg/dL, suggesting that his disorientation was due to hepatic encephalopathy. Blood tests showed that his LDH had increased to 403 IU/L whereas his ALT remained 40 IU/L. Treatment with sorafenib was stopped on that day. The next day, his encephalopathy had diminished, with a normal ammonia level and BP, while his LDH concentration had decreased to 320 IU/L. The patient has since been treated for 4 months with the same regimen (5-fluorouracil and cisplatin) of hepatic arterial infusion chemotherapy without any further sign of hepatic encephalopathy.

Patient 2

A 66-year-old man with jaundice and appetite loss was admitted to our hospital. He had been diagnosed with type-2 diabetes mellitus more than 10 years earlier. Fifteen months before admission, an HCC 8 cm in diameter was found in the left lobe of his liver. Although he underwent left lobe

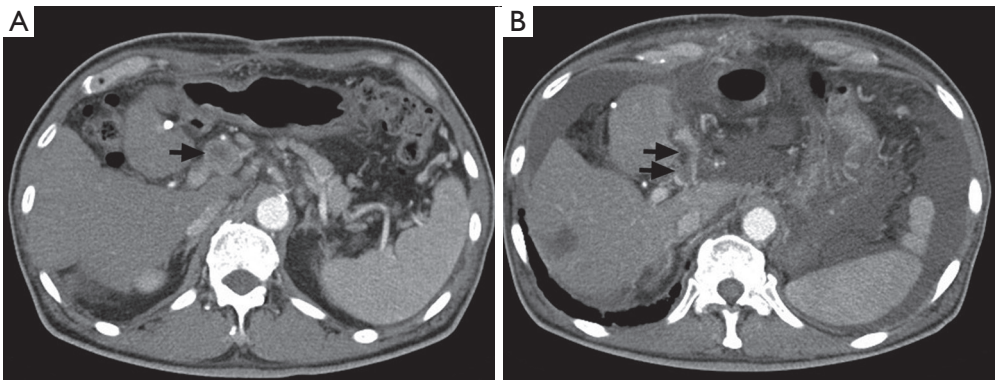

Figure 3 Contrast-enhanced CT imaging of patient 2 before (A) and after (B) sorafenib therapy. At the time of admission with jaundice, the thrombus in the portal vein extended into the intrahepatic branch. CT, computed tomography.

resection, owing to his good hepatic functional reserve, intrahepatic tumor recurrences were repeatedly observed. He underwent two sessions of transcatheter arterial chemoembolization (TACE), 11 and 7 months before admission. After the second TACE session, several lymph node (LN) metastases close to the portal vein were found, whereas no intrahepatic recurrences were observed. As radiation therapy was ineffective in treating the metastases, sorafenib (400 mg/day) treatment was subsequently started while the patient was hospitalized. Adverse events included hand-foot skin reaction, an increase of BP, and an increase in of LDH level (221 to 277 U/L). A limited blood clot thrombosis in the portal vein trunk, observed prior to sorafenib therapy, was not regarded as an obstacle to treatment. He was discharged from the hospital 7 days after sorafenib treatment, followed by continuous administration of 400 mg/day sorafenib. Seven days later, he experienced jaundice and progressive loss of appetite. Blood tests on admission showed considerable deterioration of liver function, including PT-INR of 4.97, albumin 2.4 g/dL, ALT of 777 U/L, LDH of 393 U/L, total bilirubin of 18.6 mg/dL, and direct bilirubin of 12.2 mg/dL. Doppler ultrasonography and CT examination showed the extension of portal thrombosis to the intrahepatic branches and the appearance of moderate ascites (*Figure 3*). Despite efforts to support liver function with plasma exchange, his liver size rapidly decreased, leading to fatal liver failure in 1 week.

Discussion

The anti-cancer activity of sorafenib is thought to be due to two different pathways: inhibition of the serine-threonine kinase Raf-1, which decreases mitogen-activated protein kinase kinase (MEK) and extracellular signal-regulated kinase (ERK) activity, resulting in the suppression of tumor cell proliferation; and the inhibition of kinases associated with angiogenesis, such as vascular endothelial growth factor (VEGF) receptors-2 and -3 and platelet-derived growth factor receptor β (18). As sorafenib treatment has become more widespread, so has the number of these patients experiencing increases in BP during sorafenib treatment (19). Furthermore, several patients have developed coronary artery spasm during sorafenib therapy (20-22). These adverse effects may be due to the inhibition by sorafenib of the VFGF signaling pathway, decreasing endothelial nitric oxide synthase (eNOS) expression by endothelial cells and causing vascular smooth muscle cell constriction (23). These phenomena may have played key role in the rapid development of liver failure observe in our patients.

In considering the mechanism of liver failure in our patients, we found characteristics in common with previously reported patients with HCC who achieved CR on sorafenib monotherapy (5-17). Of 15 patients, seven had portal vein tumor thrombi, two had portal thrombosis, three had tumor invasion into the inferior vena cava (IVC), two had portal LN swelling, and one had vascular-invading HCC (*Table 1*). Taken together, all of these patients had a condition that could decrease portal blood flow, strongly indicating that deterioration in portal flow is essential to achieving CR on sorafenib monotherapy. That is, sorafenib can induce CR in patients with HCC by compressing the hepatic artery following decreased portal flow, a process that could cause extreme hypoxic circumstances in the liver.

Although liver hypoxia may be indispensable for CR, the decrease of both portal and arterial blood flow might also

Table 1 Patients with HCC who experienced CR during treatment with sorafenib

Author	Year	PVTT/PVT	Other conditions
Wang *et al.* (5)	2010	PVTT	–
Abbadessa *et al.* (6)	2011	Patient 3: n.d.	Vascular-invading
		Patient 4: PVTT	–
Chelis *et al.* (7)	2011	–	Portal LN swelling
Irtan *et al.* (8)	2011	Case 1: PVTT	–
		Case 2: PVTT	–
Sacco *et al.* (9)	2011	PVT	–
Curtit *et al.* (10)	2011	–	IVC invasion
Mizukami *et al.* (11)	2012	–	Portal LN swelling
Gerardi *et al.* (12)	2013	–	IVC invasion
Kermiche-Rahali *et al.* (13)	2013	PVT	–
Kim *et al.* (14)	2013	PVTT	–
Moroni *et al.* (15)	2013	PVTT	–
Hagihara *et al.* (16)	2013	–	IVC invasion
Shiozawa *et al.* (17)	2014	PVTT	–

HCC, hepatocellular carcinoma; CR, complete remission; PVTT, portal vein tumor thrombus; PVT, portal vein thrombosis; n.d.; not described; LN, lymph node; IVC, inferior vena cava.

result in liver failure. Indeed, sorafenib was found to induce partial remission in two patients with HCC, followed by the rapid development of liver failure (24). Because sorafenib administration to patients with decreased portal flow could cause both CR and liver failure, two biomarkers of hypoxia, LDH and DCP, should be monitored during treatment with sorafenib (25,26). Better prognosis was observed in patients with low than high pretreatment LDH levels who were treated with sorafenib (25). In contrast, time to tumor progression was significantly longer in patients with high than low DCP concentrations during treatment with sorafenib (26). These conflicting results suggest that, although sorafenib-induced liver hypoxia can suppress tumor growth, it could also adversely affect prognosis when hepatic functional reserve is insufficient, an effect amplified in patients with reduced portal flow.

Patient 1 showed a marked increase in LDH on the day he developed hepatic encephalopathy, indicating that his liver was in a hypoxic condition. The simultaneous elevation in BP suggested the constriction of the systemic vascular endothelial cells. Cessation of sorafenib treatment effected a rapid improvement in encephalopathy and decreases in serum LDH and ammonia levels. The prompt reversibility of these conditions suggested that acute liver failure in this patient was due to vascular constriction, not massive hepatocyte death. The findings in patient 2 suggest that PVT, in addition to PVTT, could induce acute liver failure and that prolonged intrahepatic hypoxia could cause fatal liver failure. Patient 2 experienced portal thrombosis before sorafenib treatment, with elevated LDH concentration observed 7 days after the start of sorafenib monotherapy. Blood examination was not performed until 1 month later, when the portal thrombus had extended and his liver failure had fatally progressed. If the risk of liver hypoxia in the presence of portal thrombosis had been perceived and had been more closely observed, liver failure may have been avoided.

In conclusion, sorafenib treatment of patients with HCC and deteriorated portal flow may be a double-edged sword. Although it may lead to CR, it may also result in liver failure. Caution should be exercised in treating patients with sorafenib, especially those with inadequate hepatic functional reserve.

Acknowledgements

The authors would like to thank Ms. Keiko Nishimura for editorial support.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Yamasaki A, Umeno N, Harada S, Tanaka K, Kato M, Kotoh K. Deteriorated portal flow may cause liver failure in patients with hepatocellular carcinoma being treated with sorafenib. J Gastrointest Oncol 2016;7(3):E36-E40. doi: 10.21037/jgo.2015.10.07

