

Sorafenib plus partial splenic embolism for treatment of hepatocellular carcinoma Barcelona stage C combined with hypersplenism: a case series

Journal of International Medical Research

49(6) 1–6

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DOI: 10.1177/03000605211023351

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Abstract

Background: Sorafenib is mainly used to treat patients with hepatocellular carcinoma (HCC) Barcelona Clinic Liver Cancer (BCLC) stage C, many of whom also have severe cirrhosis. However, hypersplenism and digestive tract hemorrhage are common complications of cirrhosis, which increase the risk and difficulty of treatment.

Methods: Nineteen patients with HCC BCLC stage C with hypersplenism were treated with sorafenib plus partial splenic embolism at Chongqing University Cancer Hospital, Chongqing, China, between January 2015 and June 2018. We analyzed the therapeutic effect and clinical safety of this treatment in these patients.

Result: Hypersplenism was rectified in all patients. The incidence rates of hemorrhage and myelosuppression were 0%, and the mean survival time was 11.2 months.

Conclusion: Sorafenib plus partial splenic embolism could relieve hypersplenism and prolong survival in patients with BCLC stage C HCC.

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Keywords

Sorafenib, partial splenic embolism, hypersplenism, survival time, hepatocellular carcinoma, liver cirrhosis

Date received: 31 August 2020; accepted: 19 May 2021

Introduction

Hepatocellular carcinoma (HCC) is the seventh most common malignant tumor and the third leading cause of cancer-related death worldwide,¹ with most patients diagnosed at an advanced stage. Sorafenib is one of the main treatments for patients with HCC Barcelona Clinic Liver Cancer (BCLC) stage C, 85% of whom also have severe cirrhosis.² Patients with cirrhosis develop hypersplenism and thrombocytopenia as hepatic fibrosis progresses, while portal hypertension caused by the cirrhosis may result in massive and fatal hemorrhage of the digestive tract. Although the drug labeling does not cite low white blood cell and platelet counts as contraindications for sorafenib use, they indicate an incidence of myelosuppression of about 1% to 10%, meaning that doctors are reluctant to use sorafenib in patients with advanced liver cancer combined with hypersplenism.

It is therefore necessary to determine how to administer sorafenib safely and reduce the incidence of complications in patients with advanced liver cancer. Here, we report on a series of patients with HCC BCLC stage C combined with hypersplenism who were treated with sorafenib plus partial splenic embolism (PSE).

Patients and methods

Patients

A series of patients with HCC BCLC stage C combined with hypersplenism treated with sorafenib plus PSE at Chongqing

University Cancer Hospital, Chongqing, China, between January 2015 and June 2018, were included in the study. All patients were diagnosed according to the European Association for the Study of Liver Disease/American Association for the Study of Liver Disease criteria. The inclusion criteria were: (i) patients with HCC BCLC stage C, not suitable for trans-arterial chemoembolization (TACE), radio-frequency ablation, or other treatments; (ii) severe hypersplenism (platelets $<70 \times 10^9/L$ or white blood cells $<3 \times 10^9/L$); and (iii) Child–Pugh A or B. The exclusion criteria were: (i) incomplete follow-up data; and (ii) combined with other serious diseases. The study was approved by the ethics committee of the Chongqing University Cancer Hospital (approved 5 January 2015). All patients provided written informed consent.

Treatments

All patients were treated with PSE using the Seldinger technique. A 4.0 French catheter was inserted into the femoral artery, the main splenic artery was located by celiac arteriography, and the blood supply to the spleen was revealed by splenic arteriography. We then performed non-selective splenic embolization of the splenic artery using 300 to 500 μm microspheres, with an area of splenic embolization $>60\%$.³ All patients were treated with prophylactic antibiotics.

The patients' conditions were evaluated 2 weeks after PSE. Enhanced computed tomography (CT) was used to determine if

the splenic infarction rate was >60%, and white blood cell and platelet counts were confirmed to be normal. Sorafenib administration was then started at a conventional dose of 0.4 g twice daily, and adjusted according to patient tolerance. Sorafenib was stopped if the blood cell counts decreased or if liver function deteriorated to Child–Pugh C.

Assessments

All patients were reviewed monthly. The reviews included measurements of alpha fetoprotein, protein induced by Vitamin K absence or antagonist-II, enhanced CT of the upper abdomen, white blood cell and platelet counts, hemoglobin, albumin, prothrombin time–international normalized ratio, total bilirubin, and Child–Pugh score. All patients were observed and

followed-up for postoperative complications, improvements of hypersplenism, adverse reactions during sorafenib treatment, and survival time from the beginning of PSE to the end of sorafenib treatment.

Statistical analysis

Data were expressed as mean \pm standard deviation, median (interquartile range), or frequency (%). Clinical indexes before and after treatment were compared by paired *t*-tests, and $P < 0.05$ was considered statistically significant.

Results

The patients' baseline clinical information is shown in Table 1. The symptoms of hypersplenism, including platelet count and white blood cell count, improved

Table 1. Baseline patient characteristics.

Number	Age (years)	Sex	Etiology	C–P score	MPVTT	Extrahepatic metastasis	White blood cells ($10^9/L$)	Platelets ($10^9/L$)
1	45	M	HBV	5	Y	Lung	1.5	35
2	48	F	HBV	5	Y	Bone	2.1	50
3	50	M	HBV	5	N	Lung	2.2	45
4	49	M	HBV	6	Y	N	1.9	48
5	60	M	HBV	6	N	Bone	2.3	39
6	61	M	HBV	6	Y	N	2.8	47
7	58	M	HCV	7	Y	N	2.4	36
8	43	F	HBV	7	N	Bone	1.4	52
9	53	M	HBV	6	N	Lung	2.3	53
10	49	M	HBV	6	Y	N	2.5	49
11	60	M	NBNC	5	N	Bone	1.9	46
12	62	M	HBV	7	N	Lung	2.1	58
13	57	M	HBV	7	Y	N	2.6	46
14	59	M	HBV	7	Y	Lung	2.9	40
15	60	M	HBV	6	N	Bone	2.5	50
16	58	M	HBV	7	N	Lung	2.6	37
17	61	M	NBNC	7	Y	Lung	3.1	60
18	43	M	HBV	6	N	Lung	2.4	45
19	55	M	HBV	7	N	Lung	2.6	50
Mean	54.5 \pm 6.5			6.2 \pm 0.8			2.3 \pm 0.4	46.6 \pm 6.9

M, male; F, female; N, no; Y, yes; MPVTT, main portal vein tumor thrombus; C–P score, Child–Pugh score, HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-B, non-C hepatocellular carcinoma.

significantly after treatment ($P < 0.05$), but the Child–Pugh score remained unchanged (Table 2). All patients developed fever (temperature 37.8–39.3°C) after PSE, and 15 patients developed left upper abdominal pain requiring analgesic treatment (visual analog score: 3–7). Two patients developed left pleural effusion and one had pneumonia. The adverse events are listed in Table 3. All patients received sorafenib treatment. The most common adverse event was hand–foot syndrome, which was relieved by external application of traditional Chinese medicine. There were no incidences of hemorrhage or myelosuppression throughout the treatment period, and no severe adverse events requiring sorafenib dose reduction. The mean survival time was 11.2 months.

Discussion

HCC patients with cirrhosis with severe thrombocytopenia are at high risk of bleeding and death, while this hematologic abnormality can also adversely affect the critical treatment of HCC by limiting the patient's treatment options and delaying planned diagnostic or therapeutic procedures.⁴ Many patients with liver cancer do not die from the cancer but from complications of liver cirrhosis, and patients with advanced liver cancer complicated with cirrhosis should thus be treated for cirrhosis, as well as cancer. In addition, patients with elevated blood pressure following sorafenib administration may be at significantly

increased risk of bleeding due to hypertension, as soon as within the first day after initiating therapy.^{5,6} A previous study found incidences of hypertension in HCC patients treated with sorafenib of 18.8% and 2% for all levels and levels 3/4, respectively, according to the Common Terminology Criteria for Adverse Events.⁷ However, Kim et al. showed that PSE combined with TACE effectively induced and maintained improvements in thrombocytopenia and reduced the need for platelet transfusion.⁸ PSE has been reported to be effective not only for improving cytopenia, but also for enhancing hepatic functional reserve and hepatic protein synthesis by decreasing splenic blood flow and increasing hepatic artery and superior mesentery artery blood flow.^{9,10} Moreover, PSE can induce activation of host immunity¹¹ and promote anti-tumor effects. PSE is thus an important treatment for liver cancer patients with cirrhosis.

Table 3. Complications of partial splenic embolism

Complication	N
Pain	15
Splenic abscess	0
Fever	19
Pneumonia	1
Pleural effusion	2
Hematoma	0
Hemorrhage	0
Ascites	0

Table 2. Changes in platelet count, white blood cell count, and Child–Pugh score during treatment

	Pre-treatment level	After 2 weeks		After 1 month		After 3 months	
		Level	<i>P</i> value	Level	<i>P</i> value	Level	<i>P</i> value
Platelet count ($10^9/L$)	46.6 ± 6.9	190.0 ± 65.4	<0.0001	254.6 ± 97.9	<0.0001	158.3 ± 41.8	<0.0001
White blood cells ($10^9/L$)	2.3 ± 0.4	11.3 ± 2.3	<0.0001	7.5 ± 1.5	<0.0001	4.8 ± 1.1	<0.0001
Child–Pugh score	6.2 ± 0.8	6.0 ± 0.8	0.16	5.9 ± 0.9	0.29	6.5 ± 1.0	0.31

In this study, we included patients with distant metastasis of liver cancer or main portal vein tumor thrombosis. Sorafenib is the only recommended treatment for these patients according to BCLC stage, because the disease is too advanced and TACE cannot be administered because of portal venous embolism. However, we additionally administered PSE to patients in the current study, and showed that both white blood cells and platelets returned to normal levels after PSE, indicating that the hypersplenism was significantly improved. Furthermore, there were no changes in liver function and no gastrointestinal bleeding during the subsequent use of sorafenib. The main complications of PSE were fever and pain, but these generally only lasted for 3 to 5 days and recovered after symptomatic treatment, and all patients showed good tolerance to the treatment.

The average survival time of the patients in this study was 11.2 months, compared with Bruix et al.'s analysis, which showed a median overall survival of 9.7 months in BCLC C patients treated with sorafenib.¹² PSE cannot improve the effect of sorafenib, but can reduce the mortality caused by massive hemorrhage of the digestive tract in these patients with liver cancer and cirrhosis. PSE combined with sorafenib thus has the following advantages: PSE can significantly increase white blood cells and platelets and improve hypersplenism, allowing doctors to use sorafenib and detect bone marrow suppression after sorafenib, while portal vein pressure can be reduced by splenic embolization, thereby reducing the risk of end-stage bleeding.

This study had some limitations. This was a single-center study with a small number of cases. Furthermore, the risk of complications meant that it was not possible to include a comparative group treated with sorafenib alone.

In conclusion, sorafenib plus PSE can relieve hypersplenism and prolong survival in patients with HCC BCLC stage C. PSE followed by sorafenib is therefore recommended in patients with advanced liver cancer with hypersplenism.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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References

1. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer* 2019; 144: 1941–1953. DOI: 10.1002/ijc.31937
2. Llovet JM and Bruix J. Novel advancements in the management of hepatocellular carcinoma in 2008. *J Hepatol* 2008; 48: S20–S37. DOI: 10.1016/j.jhep.2008.01.022
3. Shimizu H, Takatsuka K, Yoshida A, et al. Partial splenic embolization reverses insulin resistance in patients with liver cirrhosis. *Intern Med* 2009; 48: 747–751. DOI: 10.2169/internalmedicine.48.1649
4. Cai M, Huang W, Lin C, et al. Partial splenic embolization for thrombocytopenia in liver cirrhosis: predictive factors for platelet increment and risk factors for major complications. *Eur Radiol* 2016; 26: 370–380. DOI: 10.1007/s00330-015-3839-4
5. Akutsu N, Sasaki S, Takagi H, et al. Development of hypertension within 2 weeks of initiation of sorafenib for advanced hepatocellular carcinoma is a predictor of efficacy. *Int J Clin Oncol* 2015; 20: 105–110. DOI: 10.1007/s10147-014-0691-5
6. Li Y, Gao ZH and Qu XJ. The adverse effects of sorafenib in patients with

- advanced cancers. *Basic Clin Pharmacol Toxicol* 2015; 116: 216–221. DOI: 10.1111/bcpt.12365
7. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; 10: 25–34. DOI: 10.1016/S1470-2045(08)70285-7
 8. Kim NH, Kim HJ, Cho YK, et al. Long-term efficacy and safety of partial splenic embolization in hepatocellular carcinoma patients with thrombocytopenia who underwent transarterial chemoembolization. *J Korean Med Sci* 2019; 34: e208. DOI: 10.3346/jkms.2019.34.e208
 9. Ishikawa T, Kubota T, Horigome R, et al. Concurrent partial splenic embolization with transcatheter arterial chemoembolization for hepatocellular carcinoma can maintain hepatic functional reserve. *Hepatol Res* 2014; 44: 1056–1061. DOI:10.1111/hepr.12222
 10. Romano M, Giojelli A, Capuano G, et al. Partial splenic embolization in patients with idiopathic portal hypertension. *Eur J Radiol* 2004; 49: 268–273. DOI: 10.1016/S0720-048X(03)00134-7
 11. Matsukiyo Y, Nagai H, Matsui T, et al. Host immunological effects of partial splenic embolization in patients with liver cirrhosis. *J Immunol Res* 2018; 2018: 1746391. DOI: 10.1155/2018/1746391
 12. Bruix J, Raoul JL, Sherman M, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma subanalyses of a phase III trial. *J Hepatol* 2012; 57: 821–829. DOI: 10.1016/j.jhep.2012.06.014