Clinical factors related to long-term administration of sorafenib in patients with hepatocellular carcinoma

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Background: Sorafenib has been approved in the indication of unresectable hepatocellular carcinoma, but there are many cases in which administration of the drug is discontinued due to severe side effects. In this study, we compared the characteristics of patients who continued and discontinued sorafenib.

Methods: Ninety-six patients (75 men and 21 women) were initiated on sorafenib from July 2009 through September 2011. The patient characteristics of interest included gender, age, etiology, Child-Pugh classification, treatment history and frequency, and levels of α -fetoprotein, des-gamma-carboxy prothrombin, aspartate amino acid transferase, and alanine aminotransferase. Duration of administration of sorafenib and reasons for its discontinuation were compared.

Results: Median overall survival was 11.8 months. Discontinuation of sorafenib within 90 days was identified as an independent prognostic factor for overall survival on multivariate analysis ($P < 0.0001$). Transarterial chemoembolization performed six times or more ($P = 0.013$) was also identified as an independent factor contributing to discontinuation of sorafenib within 90 days in multivariate analysis. Patients who received sorafenib for ≥ 90 days had significantly longer overall survival than those who discontinued it ($P < 0.0001$).

Conclusion: Prolonged treatment with sorafenib is an important factor in achieving extended overall survival. We recommend starting sorafenib before latent liver damage has occurred as a result of too many transarterial chemoembolization procedures.

Keywords: sorafenib, hepatocellular continuation, discontinuation, efficacy

Introduction

In general, hepatocellular carcinoma in its early stages can be treated by surgical resection, radiofrequency ablation,^{1,2} or liver transplantation when there is a single nodule ≤ 5 cm or three nodules ≤ 3 cm (Milan criteria).³ However, many people are diagnosed in the advanced stages, when only transcatheter arterial infusion chemotherapy and transarterial chemoembolization are performed,^{4,5} but despite recently improved embolization devices,⁶ even these therapies have limited success in cases of vascular invasion or extrahepatic spread.⁷ Because hepatocellular carcinoma has a high recurrence rate, it is important to prevent secondary disease, and several therapies have been reported to prevent recurrence, including interferon,⁸ retinoids,⁹ and branched-chain amino acids.¹⁰

Recently, a number of molecularly targeted agents have been investigated throughout the world,^{11–13} and some agents are entering Phase II or III trials.^{14,15} Sorafenib inhibits the serine/threonine kinases, RAF-1 and B-Raf,^{16,17} inhibits the tyrosine kinase activity of vascular endothelial growth factor receptors 1, 2, and 3 and

platelet-derived growth factor receptor β ,^{16,17} which has been shown to trigger production of reactive oxygen species and death of hepatocellular carcinoma cells.¹⁸

Sorafenib was approved to treat hepatocellular carcinoma in 2007,¹⁹ and is used in patients with advanced stage disease. In two well known studies, sorafenib significantly increased survival time in patients with hepatocellular carcinoma, although there were absolute differences in survival time between the two patient populations because the definition of advanced disease differed between the two studies.^{20,21}

Although administration of 800 mg of sorafenib is recommended, there are many cases in which administration is discontinued or the dosage is reduced because of severe side effects.^{15,20,22} In this study, we demonstrated the therapeutic effects of sorafenib retrospectively and compared the characteristics of patients who continued and discontinued treatment with this agent.

Materials and methods

Patients

We enrolled 96 patients who had started to receive the drug in our hospital or at one of six affiliated hospitals from July 2009 through September 2011 and were able to be observed for more than 90 days. The patient characteristics investigated included gender, age, etiology, Child-Pugh classification, treatment history and frequency, levels of α -fetoprotein, des-gamma-carboxy prothrombin, aspartate amino acid transferase, and alanine aminotransferase, as well as treatment received prior to administration of sorafenib, eg, surgery, percutaneous ethanol injection therapy, percutaneous microwave coagulation therapy, radiofrequency ablation, transarterial chemoembolization, transcatheter arterial embolization, and/or transcatheter arterial infusion. The effectiveness of the treatments was evaluated according to modified Response Evaluation Criteria In Solid Tumors (RECIST)²³ using an enhanced computed tomography scan every 3 months. Duration of administration of sorafenib was noted and the reasons for its discontinuation were identified.

Treatment plan and toxicity evaluation

Sorafenib was initiated at 800 mg/day in two divided doses,²⁴ and dose reduction was allowed for unacceptable adverse effects, ie, grade 3/4 toxicities, and treatment was continued until disease progression, development of intolerable drug toxicity, or patient refusal to continue taking the drug. Patients were followed up on an outpatient basis every 2–4 weeks. Adverse events were assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0.

Statistical analysis

Overall survival was estimated using the Kaplan-Meier method, and differences in survival between the groups were compared using the log-rank test. Cox's proportional hazard model and logistic regression were used to examine likely prognostic factors in each group. The results were reported as hazard ratios with 95% confidence intervals. $P < 0.05$ was considered to be statistically significant for all analyses. All statistical analyses were performed using JMP version 7.2 software (SAS Institute, Cary, NC).

Results

Patient characteristics

The 96 patients comprised 75 men and 21 women of mean age of 71.2 ± 16.8 (median 71) years (see Table 1). The etiology was hepatitis C virus in 56, hepatitis B virus in 15, and others in 25. Median (range) levels of

Table 1 Baseline patient characteristics and previous therapy before administration of sorafenib

Variable	Median (range)
Age	71 (52–87)
Gender (M/F)	75/21
HCV/HBV/others	56/15/25
Aspartate transaminase (U/L)	54 (19–165)
Alanine aminotransferase (U/L)	33 (12–150)
Platelets (per μ L)	12 (5–32)
α -fetoprotein (ng/mL)	88.7 (3.2–245,500)
des-gamma-carboxy prothrombin (mAU/mL)	559 (5–75,000)
Child-Pugh classification (5/6/7)	62/30/4
BCLC stage B/C	37/59
Extrahepatic spread ($\pm$)	27/69
Macroscopic vascular invasion ($\pm$)	30/66
ECOG performance status (0/1/2)	50/44/2
Previous therapy	n (%)
Operation	32 (33)
Percutaneous ethanol injection therapy	11 (11)
Percutaneous microwave coagulation therapy	1 (1)
Radiofrequency ablation	42 (44)
TA(C)E	72 (75)
Transcatheter arterial infusion	19 (20)
Radiation	5 (5)
Efficacy in all patients	
Level of response	n (%)
CR	0 (0)
PR	13 (14)
SD	31 (32)
PD	30 (31)
Not evaluable	22 (23)
Response rate	14%
Disease-control rate	46%

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TACE, transarterial chemoembolization.

α -fetoprotein, des-gamma-carboxy prothrombin, aspartate (U/L), and alanine aminotransferase (U/L) were 88.7 (3.2–245,500) ng/mL, 559 (5–75,000) mAU/mL, 54 (19–165) IU/L, and 33 (12–150) IU/L, respectively. Fifty, 44, and two patients had an Eastern Cooperative Oncology Group performance status of 0, 1, and 2, respectively. Child-Pugh classification was 5 in 62, 6 in 30, and 7 in four. Barcelona Clinic Liver Cancer (BCLC) staging was B in 37 and C in 59. Twenty-seven patients had metastatic disease in organs other than the liver. Prior medical history at the time of initiation of sorafenib therapy was surgery in 32, percutaneous ethanol injection therapy in 11, percutaneous microwave coagulation therapy in one, radiofrequency ablation in 42, transarterial chemoembolization and/or transcatheter arterial embolization in 72, transcatheter arterial infusion in 19, and radiation in five cases.

Efficacy, response, and disease control rates

Median overall survival was 11.8 months. No patients had a complete response, 13 patients (14%) had a partial response, and 31 (32%) had stable disease (according to modified RECIST criteria), whereas 30 patients (31%) had progressive disease and 22 patients were not evaluable. The disease control rate was 46% and the response rate was 14% (see Figure 1 and Table 1).

Compliance with treatment

The mean sorafenib dose was 800 mg in 26 patients (27%), 600 mg in nine (9%), 400 mg in 46 (48%), and ≤ 200 mg in 15 (16%). Because the median duration of treatment was 87 (range 2–737) days, we divided the patients into two

groups, ie, one with ≥ 90 days of treatment with sorafenib ($n = 45$) and another within 90 days of treatment with sorafenib ($n = 51$), and examined factors influencing the patient's ability to take the drug on a longer-term basis (Table 2). Common reasons for discontinuation within 90 days were adverse events (40 patients) and radiologic progression ($n = 11$). The adverse events were hand-foot skin reactions ($n = 3$), diarrhea ($n = 3$), general fatigue ($n = 2$), rash ($n = 3$), fever ($n = 3$), renal failure ($n = 2$), pancreatitis ($n = 1$), liver dysfunction ($n = 15$), and others ($n = 8$), whereas severe liver dysfunction included liver failure ($n = 7$), hepatic encephalopathy ($n = 3$), ascites ($n = 3$), elevation of aspartate or alanine aminotransferase ($n = 1$), and jaundice ($n = 1$).

Prognostic factors for overall survival by univariate and multivariate analysis

On univariate analysis, BCLC (C) staging ($P = 0.04$), tumor volume $\geq 50\%$ of the liver ($P < 0.0001$), macroscopic vascular invasion ($P = 0.006$), and discontinuation of sorafenib administration within 90 days ($P < 0.0001$) were significant prognostic factors, but only discontinuation of sorafenib within 90 days was identified as an independent prognostic factor contributing to overall survival on multivariate analysis ($P < 0.0001$, Table 3).

Relationship between administration for ≥ 90 days and overall survival

In the group that continued on sorafenib for ≥ 90 days, overall survival was significantly longer than in the group that discontinued sorafenib within 90 days ($P < 0.0001$), and the same relationship was found in the 61 patients who had their dose reduced to 400 mg and 200 mg ($P = 0.0026$,

Figure 1 Overall survival for all patients.

Note: Median overall survival was 11.8 (range 7–763) days.

Table 2 Reasons for discontinuation of sorafenib within 90 days

Adverse events without liver dysfunction	36
Progressive disease	11
Hand-foot skin reaction	3
Diarrhea	3
General fatigue	2
Rash	3
Fever	3
Renal failure	2
Pancreatitis	1
Others	8
Liver dysfunction	15
Liver failure	7
Hepatic encephalopathy	3
Ascites	3
Elevation of AST or ALT	1
Jaundice	1

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase.

Table 3 Risk factors contributing to overall survival (n = 96)

	Subgroup	Univariate analysis			Multivariate analysis		
		Risk ratio	95% CI	P value	Risk ratio	95% CI	P value
Age	≥71 or <71	0.74	0.39–1.41	0.36			
Gender	Female	1.53	0.94–2.51	0.08			
Child-Pugh classification	≥6 or 5	0.54	0.28–1.04	0.06			
α-fetoprotein (ng/mL)	<50 or ≥50	1.95	0.94–4.0	0.71			
Des-gamma-carboxy prothrombin (mAU/mL)	<400 or ≥400	1.69	0.85–3.3	0.13			
Etiology	HCV, others	0.74	0.39–1.41	0.37			
PS	≥1 or 0	0.66	0.35–1.27	0.22			
BCLC	C or B	0.46	0.22–0.97	0.04	0.96	0.38–2.45	0.94
RFA	0 or ≥1	1.25	0.65–2.40	0.51			
TACE	<6 or ≥6	1.5	0.74–3.03	0.26			
Tumor volume of liver	<50% or ≥50%	4.41	2.24–8.69	<0.0001	1.70	0.77–3.74	0.19
Macroscopic vascular invasion	None or +	3.06	1.61–5.82	0.006	1.76	0.75–4.09	0.19
Discontinuation	<90 or ≥90	0.1	0.04–0.26	<0.0001	0.13	0.05–0.34	<0.0001
Extrahepatic spread	None or +	1.61	0.83–3.13	0.16			

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

Figures 2 and 3). Therefore, we concluded that treatment with sorafenib for ≥90 days achieves better overall survival, even at a reduced dose.

Risk factors for discontinuation of sorafenib within 90 days by univariate and multivariate analysis

To identify risk factors for discontinuation of sorafenib within 90 days, patients whose observed periods were less than 90 days were eliminated. The total number was 82, with 45 being ≥90 days and 37 being <90 days (Table 4). On univariate analysis, des-gamma-carboxy prothrombin (≤400 mAU/mL, $P = 0.04$), tumor

volume ≥ 50% of the liver ($P = 0.02$), macroscopic vascular invasion ($P = 0.03$), and six or more transarterial chemoembolizations ($P = 0.02$) were significant factors, and tumor volume ≥ 50% of the liver ($P = 0.04$) and six or more transarterial chemoembolizations ($P = 0.013$) were identified as independent risk factors on multivariate analysis.

Discussion

Sorafenib is considered a drug that should be used for advanced hepatocellular carcinoma, but there are no suitable criteria for treatment of hepatocellular carcinoma at this stage, because the treatment outcomes are affected by multiple variables, including liver function, patient performance status, and tumor stage.^{25,26}

Figure 2 Relationship between continuation of administration and overall survival. **Note:** In the group that continued administration for ≥90 days, overall survival was significantly higher than in the group that discontinued administration within 90 days.

Figure 3 Relationship between continuation of administration and overall survival in patients receiving 200 mg or 400 mg. **Note:** In the group that continued administration for ≥90 days, overall survival was significantly higher than in the group who discontinued administration within 90 days.

Table 4 Risk factors contributing to discontinuation of sorafenib administration within 90 days (n = 82)

	Subgroup	Univariate analysis			Multivariate analysis		
		Risk ratio	95% CI	P value	Risk ratio	95% CI	P value
Child-Pugh classification	≥6 or 5	2.10	0.83–5.30	0.11			
α-fetoprotein (ng/mL)	<50 or ≥50	0.55	0.22–1.35	0.19			
DCP (mAU/mL)	<400 or ≥400	0.39	0.16–0.97	0.04	0.59	0.22–1.60	0.30
Radiofrequency ablation	0 or ≥1	0.78	0.32–1.88	0.58			
Tumor volume of liver	<50% or ≥50%	0.08	0.01–0.69	0.02	0.99	0.01–0.91	0.04
Macroscopic vascular invasion	None or +	0.33	0.12–0.87	0.03	0.46	0.15–1.39	0.17
TACE	<6 or ≥6	0.26	0.08–0.83	0.02	0.21	0.06–0.72	0.013
Extrahepatic spread	None or +	1.81	0.67–4.92	0.24			

Abbreviations: CI, confidence interval; DCP, des-gamma-carboxy prothrombin; TACE, transarterial chemoembolization.

Many trials have reported on the use of sorafenib to prevent hepatocellular carcinoma recurrence after treatment.²⁷ Sorafenib is used with sirolimus or with inhibitors of mammalian target of rapamycin²⁹ to reduce the risk of recurrence of hepatocellular carcinoma after liver transplantation,²⁸ and it has been reported that such combination therapy can be effective. Some adjuvant therapy studies after curative treatment for hepatocellular carcinoma, such as the STORM (Sorafenib as adjuvant Treatment in the prevention Of Recurrence of hepatocellular carcinoma) trial, are ongoing,²⁷ and concurrent treatment of hepatocellular carcinoma with conventional transarterial chemoembolization and sorafenib has demonstrated a longer time to progression and possible efficacy.^{30,31} The overall median survival of our subjects was 11.8 months. Our data are slightly more robust than those of the Phase III SHARP (Sorafenib in Advanced Hepatocellular Carcinoma Assessment Randomized Protocol) trial (10.7 months)²⁰ and the tandem study in the Asia-Pacific region (6.5 months), probably because our study included a higher number of BCLC stage B patients than were included in the registration trials.²¹

Sorafenib has several side effects and is often discontinued when their grade becomes severe. Multikinase inhibitors such as sorafenib have unique clinicopathologic consequences, including hand-foot skin reactions and severe side effects.^{32–34} The severity of hand-foot skin reactions is dose-related and depends on the duration, dosage, and accumulation of the drug.³⁵ Our data show that almost all patients had side effects, with about 40% of patients discontinuing sorafenib due to adverse events. However, some side effects may predict a response to sorafenib, such as early skin toxicity and diarrhea,^{22,36–38} and methods have been reported for evaluating efficacy and overall survival.^{39,40} No studies have reported the efficacy of treatment dose or duration because the Phase III trial for sorafenib used only 800 mg.²⁰ Okuwaki et al reported late-onset progressive disease, indicating that prolonged treatment with sorafenib may be beneficial.⁴¹ In our data,

several factors in univariate analysis, such as BCLC stage C, tumor volume ≥ 50% of the liver, macroscopic vascular invasion, and discontinuation of sorafenib within 90 days reduced overall survival, but discontinuation of sorafenib within 90 days was the only factor found to reduce overall survival in multivariate analysis. Patients able to take sorafenib for longer than 90 days had better overall survival than those who discontinued within 90 days, even if they could take only 400 mg or less than 400 mg because of side effects. Our data demonstrate the benefit of a long duration of treatment, even in cases of reduced dosage. Interestingly, upon further investigation of patients who could be observed for 90 days or more, multivariate analysis showed that a tumor volume occupying ≥50% of the liver and six or more transarterial chemoembolization procedures prior to initiation of sorafenib were significant prognostic indicators. Our data indicate that prolonged administration is an important factor in obtaining good overall survival, and is better started when the number of transarterial chemoembolizations is less than six. Many transarterial chemoembolization procedures can worsen liver function and, although the Child-Pugh score does not change, there might be latent liver damage.

Sorafenib is indicated for patients with BCLC stage C and transarterial chemoembolization is recommended for patients with BCLC stage B,^{7,42} so sorafenib is usually used in patients whose tumors are progressing despite locoregional therapy. We recommend starting sorafenib before latent liver damage has occurred as a result of too many transarterial chemoembolization procedures, and prolonged administration of sorafenib is important for long overall survival, even if the dose of sorafenib needs to be reduced because of side effects.

Disclosure

The authors declare that they do not have anything to disclose regarding funding or conflicts of interest with respect to this manuscript.

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