Original Article

Survival Outcomes of Metastatic/Unresectable Hepatocellular Carcinoma in Patients Treated with Sorafenib

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Background: Hepatocellular carcinoma (HCC) is a common cancer in the Asia-Pacific region due to the high incidence of chronic viral hepatitis B (HBV) in the region. Several studies have reported a lower survival rate among patients in the Asia-Pacific region compared to patients in North America, possibly due to sorafenib being less efficacious in an Asian HBV population. There is no survival data available for patients in Thailand.

Materials and Methods: We retrospectively reviewed the clinical outcomes of 83 metastatic/unresectable HCC patients treated between January 2008 and September 2013 with sorafenib and compared their survival with different prognostic factors.

Results: In total, 83 patients were identified who had started treatment for metastatic/unresectable HCC with sorafenib. The median age of the patients was 56 years, and 85% were male. Fifty-one percent of the patients had extra-hepatic disease at the time sorafenib was indicated. Chronic HBV was found in 68% of the patients. The most common reason for discontinuation of treatment was progressive disease. The most frequently occurring grade 3 toxicities were hand-foot-syndrome (9.6%) and diarrhea (7.2%). The median overall survival was 6.3 months (95% confidence interval [CI] 3.15 to 9.15). The 6-month overall survival rate was 53%, while the median progression-free survival was 2.88 months (95% CI 2.20 to 3.45). We identified that macro-vascular invasion, elevation of alanine aminotransferase (ALT), serum alkaline phosphatase above the normal limit, serum albumin level below 3.5 g/dL, lesions in both lobes of the liver, and total bilirubin greater than 1.5 mg/dL were related to poorer overall survival.

Conclusion: The clinical outcome and toxicities profiles of sorafenib used among patients in Thailand are consistent with the previous large randomized controlled studies reported in the literature. Sorafenib is an appropriate treatment for HCC and is well tolerated by patients.

Keywords: HCC, Hepatocellular carcinoma, HCC, metastasis, Outcome, Sorafenib, Unresectable

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Hepatocellular carcinoma (HCC) is a common cause of cancer death. The 1-year survival rate of untreated patients is less than 50%[1-3] in the advanced stage. The global incidence of HCC ranges from 6.8 to 116.6 cases per 100,000 person-years for men, and 2.2 to 74.8 cases per 100,000 person-years for women. Over 80% of HCCs occur in developing countries in sub-Saharan Africa, Southeast Asia, and East Asia due to the high prevalence of viral hepatitis B and C infections. By contrast, the incidence of HCC is lower in developed countries, such as North America[4]. Before 2007, the treatment of unresectable/metastatic HCC used to involve multimodality approaches, including surgery, radiation, embolization, and systemic chemotherapy, but typically with an unsatisfactory clinical outcome[5,6].

The US FDA approved sorafenib as a standard treatment for unresectable/metastatic HCC based on the results of two phase III studies published in 2007, the SHARP[7] and Asia-Pacific trials[8], which showed the survival benefit of sorafenib over a placebo. The first study (SHARP trial) was conducted in North America and Europe and compared the efficacy of sorafenib with a placebo in unresectable/metastatic HCC patients with no prior systemic therapy. The overall survival was 10.7 months in the sorafenib group versus 7.9 months in the placebo group, while the progression-free survival was 5.5 months versus 2.8 months. In the Asia-Pacific trial, which involved patients with characteristics similar to patients in a Thai population in terms of their ethnicity and incidence of chronic viral hepatitis infection, the overall survival was 6.5 months in the sorafenib group versus 4.2 months in the placebo group, while the progression-free survival was 2.8 months versus 1.4 months, respectively.

We designed this retrospective study to assess the

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clinical outcome and clinical factors affecting the survival of metastatic/unresectable HCC patients treated with sorafenib in our institute.

Materials and Methods

We retrospectively reviewed the clinical outcomes of 83 metastatic/unresectable HCC patients treated with sorafenib between January 2008 and September 2013. The data were collected from Siriraj Hospital electronic database. Because there was no standard chemotherapy treatment for metastatic/locally advanced HCC before 2007, the first year of sorafenib approval, some patients had received systemic chemotherapy. Therefore, we included all patients who were treated with sorafenib since January 2008, as the date when sorafenib was approved in Thailand, even if they had had prior systemic therapies.

We recorded each patient's age, gender, ECOG (Eastern Cooperative Oncology Group) performance status, extension of disease, hepatitis profile, tumor markers, blood chemistry, details of previous treatments, starting date of sorafenib treatment, administrative details, adverse events, response to treatment, date of disease progression, date of last sorafenib taken, subsequent treatment, date of last follow-up, and date of death. The definition of progression-free survival (PFS) is the interval between the date of sorafenib being taken and the date of disease progression according to the RECIST (response evaluation criteria in solid tumors) criteria (the newest version at the time of assessment), which is determined by individual medical oncologist, or the physician's decision (regarding clinical progression and elevation of tumor marker that resulted in the discontinuation of treatment) or death (whichever occurred first). The response to treatment was based on the RECIST criteria. The disease control rate (DCR) is defined as a complete response, partial response, or stable disease. The overall survival (OS) is the interval between the date of sorafenib being taken and the death of date by any causes, and was obtained by retrieving the data from the Civil Registration Database at February 01, 2014. The follow-up period is the interval between the date of sorafenib being taken and the death at last follow-up in medical records. The primary objective was to determine overall survival. The secondary objective was to determine the progression-free survival, treatment response, toxicity (using NCI CTCAE v.3.0)[9], and correlation between clinical factors and death.

Statistical analysis

Patient characteristics are described herein using descriptive statistics, including the frequency and percentage for categorical variables. Continuous variables used are the mean and median with the maximum and minimum. The Kaplan-Meier method was used to estimate survival and the Log-rank test was used for univariate analysis to evaluate the effect of the baseline characteristics on survival. For univariate analysis, independent variables that potential related to survival outcome were selected from pretreated demographic data, laboratory value and severity of HCC. Multivariate analysis was performed using Cox proportional hazard model after variables in univariate analysis was determined statistically significant ($p<0.05$). All the statistical analyses were done using SPSS software, version 21.0.

Results

Clinical characteristics

Between January 2008 to September 2013, 83 patients were treated with sorafenib for metastatic/unresectable HCC at Siriraj Hospital, comprising 71 males and 12 females, with a median age of 56 years old (range 29 to 81 years old). Chronic HBV was found in 68% of the patients. Extra-hepatic disease was found in 51%. The majority of patients had ECOG 0 to 1. Macro-vascular invasion was found in about 50.6%. Patients without cirrhosis accounted for 15.7% of the total, while Child-Pugh class A was 77%. All of the patients with available ALBI (albumin-bilirubin) grading were grade 1. The median MELD (Model for End-Stage Liver Disease) score was 6.79 (6.43 to 27.46). Alpha-fetoprotein (AFP) value above the normal limit was found in 71% of the patients, while 54% of patients had a confirmed diagnosis of HCC by tissue pathology. Prior chemotherapy treatment was undertaken by 9.6% of the patients. The baseline characteristics of all the patients are described in Table 1.

Compliance

Most patients were prescribed a dosage of sorafenib at 800 mg per day. Sixty-four percent of them were able to tolerate a full dosage of sorafenib until complete treatment. The median time of sorafenib administration was 2.3 months (0.03 to 50.2). Sixty-seven percent of patients had a duration of taking a full dose of longer than 1 month, while 29% of patients required a dose reduction within the first month of administration. The most frequently recorded reasons for the discontinuation of treatment were progressive disease and patient decision, which occurred in 59% and 14% of cases, respectively. We found that 12% of them had developed a contraindication against the drug administration during treatment.

Response

Among the 83 patients who received sorafenib, 6 patients had never been assessed by imaging. Therefore, only 77 patients were included in the analyses to obtain the best response. The disease control rate was 49%. Thirty-five (45.8%) patients had stable disease and three patients (3.6%) achieved a partial response. There was no complete response found in any of the records we checked.

Toxicity

The incidence of treatment-related adverse events of any grade was 51.8%. The most common adverse events were hand-foot syndrome (HFS; 33.7%), diarrhea (22.8%), and fatigue (15.7%). The most common grade 3 to 4 toxicities were HFS (9.6%) and diarrhea (7.2%). One of patients had grade 3 hypertension, while another two patients had grade 3

Table 1. Clinical characteristics of patients with unresectable/metastatic HCC

Clinical characteristics	Number (%)
Median age, years (range)	56 (29 to 81)
Gender	
Male	71 (85.5)
Female	12 (14.5)
ECOG	
0 to 1	43 (51.8)
2	2 (2.4)
Locally advanced disease	36 (43)
Extrahepatic spreading	44 (5)
Lungs	36
Bone	7
Peritoneal cavity	3
Lymph node	2
Others	5
Liver lesion(s)	
Right lobe	25 (30.1)
Left lobe	8 (9.6)
Both lobes	39 (47)
Macrovascular invasion	
No	37 (44.6)
Yes	42 (50.6)
Pathology diagnosis	
No	38 (45.8)
Yes	45 (54.2)
Hepatitis virus status	
Hepatitis B	57 (68.7)
Hepatitis C	11 (13.3)
No cirrhosis	13 (15.7)
Cirrhosis Child-Pugh class	
A	64 (77.1)
B	3 (3.6)
Missing data	16 (19.2)
MELD score	
<10	61 (73.5)
≥10	5 (6.0)
Missing data	17 (20.5)
Alpha-fetoprotein >UNL	59 (71)
Alanine transaminase >3 xUNL	22 (26.5)
Total bilirubin ≥1.5 mg/dL	12 (14.4)
ALBI (Albumin-Bilirubin) grade	
Grade 1	77 (92.8)
Grade 2 and 3	0 (0)
Missing data	6 (7.2)
Prior systemic therapy	8 (9.6)

Data are expressed in number (%) unless specified
UNL = upper normal limit

bleeding and grade 3 rash, respectively. The most common toxicities resulting in dose reduction were HFS (23.7%) and diarrhea (10%). No treatment was related to death.

Subsequent treatment

Twenty-three percent of patients had further treatment after disease progression. The majority of those patients received chemotherapy and targeted therapy in a clinical trial, accounting for 11.8% and 5.3%, respectively.

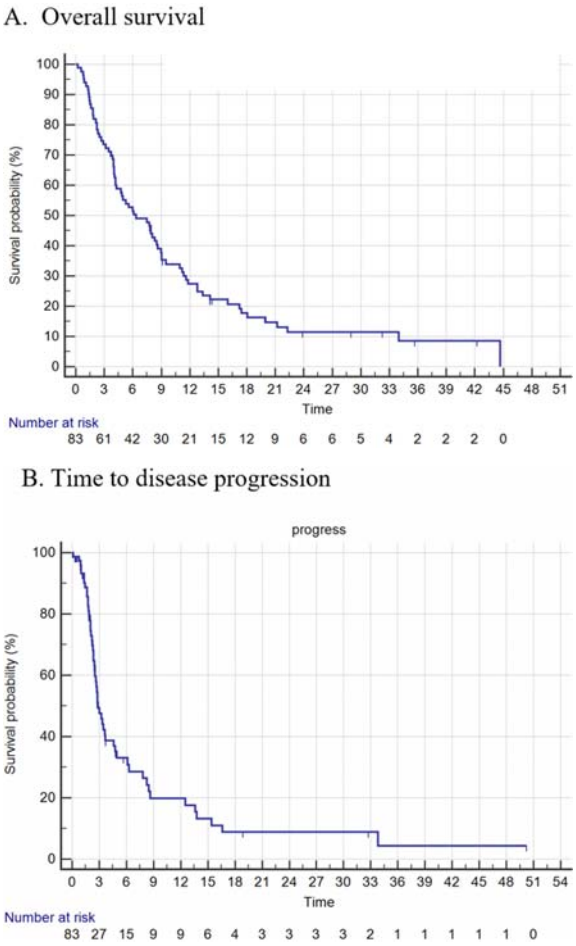

Figure 1. Overall survival (A) and time to disease progression (B) of metastatic/unresectable HCC patients treated with sorafenib

Survival

The median follow-up time was 3.7 months (range 0 to 44.7). At follow-up, 11 patients were still alive, while 72 patients had died. Overall survival was 53% at 6 months. The median overall survival was 6.3 months (95% CI 3.2 to 9.2), while progression-free survival was 2.8 months (95% CI 2.20 to 3.45) (Figure 1).

Univariate analysis was performed between the baseline characteristics and the survival rate. We identified that macro-vascular invasion, ALT (alanine aminotransferase) more than 3 times above the normal upper limit (UNL), serum alkaline phosphatase above UNL, serum albumin level below 3.5 mg/dL, lesion in both lobes of the liver and total bilirubin greater than 1.5 mg/dl were related to poorer overall survival. While the patients who had undergone previous treatment with systemic chemotherapy and subsequent treatment were associated with greater overall survival. None of other independent factor had a significant correlation with overall survival (Table 2).

Multivariate analysis revealed the remaining significant factors correlated to survival were serum alkaline phosphatase, ALT elevation, prior chemotherapy and receiving subsequent treatment (Table 3). We also evaluated other prognostic factors, such as ECOG, extra-hepatic metastasis, level of AFP, HBV infection, and duration of full dose administration, but all those factors did not correlate to survival.

Discussion

The purpose of this retrospective study was to assess the clinical outcome and clinical factors related to the death of metastatic/unresectable HCC patients treated with sorafenib. In terms of the demographic data, patients in our institute were similar to the population in a previously reported Asia-Pacific trial of HCC patients treated with sorafenib, including the median age, sex, and performance status[8]. The severity of disease in our study was less than in the previous studies[7,8], which reported 69% of patients had extra-hepatic disease compared to only 55% in this study. The incidence of viral hepatitis in our study, though, was equal to the aforementioned Asia-Pacific trial. The overall survival in our study was also similar to the sorafenib arm of the Asia-Pacific trial.

We determined the extension of liver involvement, ALT elevation, elevated serum alkaline phosphatase, low serum albumin, high serum bilirubin, and macro-vascular invasion as prognostic factors, which were correlated to survival in previous studies[7,8]. The subgroup analysis of the Asia-Pacific trial[10] showed a survival benefit from sorafenib compared with the placebo even for patients who had HBV infection, even though a phase II study[11] and a few literature reports[12,13] suggested that HBV infection was a poorer clinical outcome and treatment was less effective, but the present study demonstrated no correlation between HBV infection and survival in the patient treated with sorafenib[14]. Although the previous studies[15-17] showed that ECOG performance status, extra-hepatic spreading, Child-Pugh class, and AFP level were prognostic factors correlated to survival, there was no relationship between those factors and survival in our study; however, only few patients with Child-Pugh B were included in this study. The severity of liver disease using MELD score was reported as an independent factor for poorer survival[18]; however, no significant correlation between MELD score (≥10 vs. <10) and survival outcome in our study possible due to very small number of the patients with MELD score ≥10. In the multivariate analysis, the elevation of serum alkaline phosphatase, ALT elevation, prior use of chemotherapy, and prior local treatment remained correlated with survival consistent with the previous study[14,17]. The elevation of alkaline phosphatase and ALT elevation were associated with a poor prognosis due to the severity of the disease. Prior chemotherapy and subsequent

Table 2. Univariate analysis of baseline prognostic factors for overall survival

Variables	Hazard ratio	95% confidence interval	*p*-value
Portal vein involvement	1.64	1.01 to 2.67	0.045
Alanine transaminase >3x UNL	2.10	1.23 to 3.60	0.006
Alkaline phosphatase >UNL	1.96	1.16 to 3.30	0.011
Albumin <3.5 mg/dL	2.31	1.29 to 4.14	0.004
Total bilirubin >1.5 mg/dL	2.86	1.45 to 5.66	0.002
Lesions involved both lobes	1.68	1.03 to 2.72	0.034
Subsequent treatment	3.33	1.79 to 6.19	0.000
Prior chemotherapy	3.28	1.29 to 8.32	0.008
Age >60 years old	1.45	0.83 to 12.34	0.91
Extrahepatic metastasis	1.48	0.77 to 2.84	0.23
HBsAg positive	0.81	0.47 to 1.38	0.45
Alpha-fetoprotein >UNL	1.53	0.81 to 2.88	0.18
MELD score ≥10	0.49	0.15 to 1.58	0.23

Data are expressed in number (%) unless specified
UNL = upper normal limit

Table 3. Multivariate analysis of baseline prognostic factors for overall survival

Variables	Hazard ratio	95% confidence interval	*p*-value
Prior chemotherapy	3.81	1.06 to 13.7	0.04
Subsequent treatment	2.28	1.16 to 4.51	0.01
Alkaline phosphatase >UNL	2.09	1.19 to 3.67	0.01
Alanine transaminase >3x UNL	1.85	1.02 to 3.34	0.04

UNL = upper normal limit

treatment were associated with longer survival, which might be due to the individual nature of the low aggressive disease and the physicians selecting further treatment in the case of physically fit patients.

The progression-free survival in the present study was also similar to that in the Asia-Pacific study[8]. Few patients in our study had apparent clinical progression, such as the development of new ascites or new lymphadenopathy without evidence of radiologic progression but resulting in the discontinuation of sorafenib by physician decision.

All grades of toxicities were recorded as a 51.8% incidence, which was lower than the incidence in other studies[7,8,17], probably due to incomplete medical records of some minor adverse events. However, grade 3/4 toxicities occurred in 19.6% of patients, which was not very different to the figure reported in previous trials. The proportion of patients who required dose reduction was also consistent with the findings in the Asia-Pacific study. The most common reason for discontinuation was progressive disease. For the majority of patients who had adverse events leading to the withdrawal of sorafenib, the reasons were jaundice and bleeding without radiologic progression of disease. Discontinuation of the drug in 2 patients was due to hand-foot syndrome and diarrhea. We noted that the percentage of patients who decided to cease sorafenib without evidence of progressive disease or serious adverse events was similar to reported in previous studies. Among those patients, 4 patients could not be followed-up, two patients experiencing grade 2 hand-foot syndrome refused to resume sorafenib at the lower dose, 2 patients developed anorexia, three of them had significant weight loss, and another two asked for a change in treatment with alternative medicine. No treatment was related to death.

The key limitation of this study is its retrospective design, in which incomplete data and the small number of patients can cause the limitation of statistical power. Progression-free survival was determined by the individual oncologist without central radiologist and could be bias in terms of treatment response. Also, the data from our institute cannot represent the general Thai population due to the reimbursement aspect related to the patient treatment, whereby only civil servants and self-pay patients can access sorafenib.

Conclusion

This is the first report of the clinical outcome and toxicities profiles of sorafenib among the metastatic/unresectable HCC patients in Thailand. The survival outcomes are consistent with the previous large randomized controlled studies reported in the literature. Receiving of subsequent treatment after sorafenib was determined to be an independent favorable factor for survival, thus second-line therapy after sorafenib could be considered. Weighing benefit of 2.8-month progression-free survival with cost of treatment should be discussed in the setting that limits access to these medicines. Sorafenib is appropriate and tolerable for unresectable/metastatic HCC in Thai population.

What is already known on this topic?

Survival outcome, prognostic factors, and drug tolerability in Asian people with unresectable/metastatic HCC treated with sorafenib have been established for a decade. Survival outcome is still poor among this certain setting.

What this study adds?

This is the first publication that demonstrates efficacy and tolerability of sorafenib in Thai population with unresectable/metastatic HCC. Therefore, this data may benefit for weighing 2.8-month progression-free survival and the cost of treatment in the setting that the drug accessibility is limited or self-pay. This study can facilitate physicians to offer second-line therapy after failure of sorafenib, since receiving of subsequent therapy was determined as a favorable prognostic factor. Survival outcome of patients treated in the large national tertiary care center was comparable to those from previous large randomized controlled trial.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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