Hand-Foot Syndrome and Post-Progression Treatment Are the Good Predictors of Better Survival in Advanced Hepatocellular Carcinoma Treated with Sorafenib: A Multicenter Study

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Keywords

Hepatocellular carcinoma · Sorafenib · Hand-foot syndrome

Abstract

Objective: To determine the relationship between treatment outcomes and hand-foot syndrome (HFS), and the relationship between survival rate and post-progression treatment after sorafenib therapy. **Methods:** The study assessed 314 patients with advanced hepatocellular carcinoma (HCC) treated with sorafenib at 5 general hospitals in Kagawa Prefecture, Japan. **Results:** At the start of sorafenib therapy, 23.6% of the patients had HCC of a Child-Pugh class other than A. The initial sorafenib dose was 800 mg in 9.2% of the patients and 400 mg in 64.3%. Time to progression was 129 days (95% CI:

87.3–170.7) and the median overall survival (OS) was 392 days (95% CI: 316.0–468.0). The OS of the patients with Child-Pugh class A HCC was significantly better than that of the patients with Child-Pugh class B HCC ($p < 0.0001$). The survival curves for Child-Pugh class A-5 points and class A-6 points were significantly different, with that for class A-5 points being better ($p < 0.0001$). A significant difference was observed between the patients who exhibited HFS and those who did not, with the former exhibiting a better survival rate ($p < 0.001$). In addition, the survival rate of the patients who received post-progression treatment after sorafenib therapy was significantly better than that of the patients who did not ($p < 0.001$). **Conclusion:** In sorafenib therapy, patients with HFS and those who received post-progression treatment exhibited good OS.

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Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer mortality in the world [1]. Sorafenib is an agent that has improved the time to progression and overall survival (OS) in advanced stages of HCC with vascular invasion and/or extrahepatic spread [2]. Sorafenib has been administered in accordance with the consensus-based treatment algorithm for HCC proposed by the Japan Society of Hepatology [3–6]. According to this algorithm, sorafenib is indicated for patients diagnosed with Child-Pugh class A HCC with extrahepatic spread or vascular invasion. Sorafenib is also recommended for patients with Child-Pugh class A HCC where transcatheter arterial chemoembolization (TACE) [7–11] and hepatic arterial infusion chemotherapy [12, 13] are not indicated. In the present study, we examined the efficacy of sorafenib treatment and the clinical outcome in 314 patients at 5 general hospitals in Kagawa Prefecture, Japan.

Subjects and Methods

Patients

Between June 2009 and January 2016, 314 patients with advanced HCC were treated with sorafenib at 5 general hospitals in Kagawa Prefecture, Japan. The diagnosis of HCC was made based on histological or radiological findings using contrast-enhanced

computed tomography and/or dynamic magnetic resonance imaging [14, 15]. The responses of all patients were evaluated using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [16].

Statistical Analyses

Univariate analysis was used to identify predictors of survival using the Kaplan-Meier method, and comparisons were performed using the log-rank test. A p value of <0.05 was considered statistically significant. All analyses were performed using SPSS version 22.0 for Windows (IBM, Armonk, NY, USA).

Results

Baseline Characteristics

The study included 254 men and 60 women. Their mean age was 72.5 ± 9.46 years (range: 38–91), their mean height was 160.4 ± 9.12 cm (range: 125.7–179.0), and their mean weight was 58.6 ± 11.9 kg (range: 27–101.9). There were 43 patients with hepatitis B virus infection, 175 patients with hepatitis C virus infection, and 96 patients with other forms of liver disease. In 57 patients, HCC had been newly diagnosed, whereas in 257 patients it had recurred. There were 295 patients with a history of treatment for HCC and 19 patients with no such history. The mean initial sorafenib dose was 391.7 ± 159 mg/day (range: 200–800).

Fig. 1. Kaplan-Meier curves of time to progression (TTP) and overall survival (OS) of patients with sorafenib treatment. MST, median survival time; mRECIST, modified Response Evaluation Criteria in Solid Tumors.

Table 1. Patient characteristics by Child-Pugh class

	Child-Pugh class A (n = 181)	Child-Pugh class B (n = 55)	p
Sex (male/female)	196/44	58/16	ns
Age (<70/≥70 years)	82/158	37/37	0.014
Height (<160/≥160 cm)	94/140	29/45	ns
Weight (<60/≥60 kg)	140/94	43/31	ns
Background (HBV/HCV/other)	33/130/77	10/45/19	ns
Initial manifestation/recurrence	39/201	18/56	ns
Tumors (<4/≥5)	114/115	29/45	ns
AFP (<200/≥200 ng/mL)	128/108	34/37	ns
DCP (<400/≥400 mAU/mL)	110/125	24/44	ns
AFP-L3 (<10/≥10%)	39/87	8/25	ns
Stage (III or lower/IVa/IVb)	106/40/94	36/18/20	ns

AFP, α-fetoprotein; DCP, des-gamma-carboxyprothrombin.

The Child-Pugh class and score at the initiation of sorafenib therapy was A-5 points in 129 patients, A-6 points in 111 patients, B-7 points in 48 patients, and B-8 points or higher in 26 patients. Sorafenib therapy was initiated in stage I in 6 patients, stage II in 51 patients, stage III in 85 patients, stage IVa in 58 patients, and stage IVb in 114 patients. The mean observation period in the present study was 223 ± 277 days (range: 2–1,665). The indications for starting sorafenib were distal metastasis in 39.8% of the patients, unresponsiveness to TACE in 39.5%, inability to perform TACE in 8.9%, severe vascular invasion in 10.8%, and other reasons in 1.0%. The lung was the site of distant metastasis in 54 patients, the bone in 39 patients, lymph nodes in 36 patients, the adrenal glands in 14 patients, and the peritoneal cavity in 13 patients (some patients had metastases to multiple sites).

OS and Radiological Evaluation

The results of sorafenib therapy were a time to progression of 129 ± 21.3 days (95% CI: 87.3–170.7) and a median OS (median survival time [MST]) of 392 ± 38.8 days (95% CI: 316.0–468.0) (Fig. 1). A complete response, partial response, stable disease, progressive disease, and incomplete evaluation were observed in 10, 25, 113, 147, and 19 patients, respectively. The overall response rate was 11.1%, and the tumor control rate was 47.4%. An initial sorafenib dose of 200 mg was administered to 77 patients, 400 mg to 202 patients (the most common dose), 600 mg to 6 patients, and 800 mg to 29 patients. The mean duration of sorafenib administration was 223.6 days, and the mean durations for the 200-, 400-, 600-, and 800-mg doses were 212.6, 242.2, 155, and 136.8 days, respectively.

Fig. 2. Kaplan-Meier curves of overall survival (median survival time [MST]) of the patients in the standard-dose group, the half-dose group, and the quarter-dose group (by initial dose).

Disparities between institutions regarding the initial sorafenib dose were observed. The survival rate with a 400-mg initial dose was significantly higher than that with an 800-mg initial dose (Fig. 2).

A significant difference in patient characteristics according to Child-Pugh class was only observed for age (<70 years, ≥70 years; $p = 0.014$); no significant differences were observed for the other variables (Table 1). Re-

Fig. 3. Survival curves by Child-Pugh class and score at the start of therapy. **a** Kaplan-Meier curves of overall survival (median survival time [MST]) of the patients with Child-Pugh class A and Child-Pugh class B hepatocellular carcinoma (HCC). There was a significant difference between class A and class B. **b** Kaplan-Meier curves of overall survival (MST) of the patients with Child-Pugh

class A-5 points and Child-Pugh class A-6 points. There was a significant difference between class A-5 points and class A-6 points. Child-Pugh class B HCC had worse results than class A HCC, but the results for class A-6 points were close to those for class B (no significant difference between class A-6 points and class B).

Fig. 4. Kaplan-Meier curves of overall survival (median survival time [MST]) of the patients with a hand-foot syndrome (HFS) side effect and those without an HFS side effect. Overall survival was significantly longer among the patients who exhibited HFS as a side effect.

garding survival rate, a significant difference was observed between Child-Pugh class A and class B, with the former being better ($p < 0.0001$). Further, OS was significantly different between Child-Pugh class A-5 points and class A-6 points, with class A-5 points being better ($p = 0.02$); however, OS was not significantly different between Child-Pugh class A-6 points and class B ($p = 0.069$). The best OS was observed when treatment was initiated at Child-Pugh class A-5 points (Fig. 3).

Next, we examined the onset of hand-foot syndrome (HFS), which is an adverse effect of sorafenib. During the observation period, HFS was observed in 118 patients (37.6%), with the mean number of days until onset being 29.6 ± 33.8 (range: 1–227). By grade, adverse effects were observed in 43 patients with grade I HCC (14.0%), 42 patients with grade II HCC (13.8%), and 24 patients with grade III HCC (7.9%). The number of days until onset of HFS was less than 1 month from initiation of sorafenib therapy for 65.3% of the patients who exhibited HFS. Regarding differences in OS based on the presence or absence of HFS, the MST of the patients with HFS was 487 days, while that of the patients without HFS was 292 days; this difference was statistically significant ($p = 0.001$) (Fig. 4). The MSTs of the patients who underwent post-

Fig. 5. Kaplan-Meier curves of overall survival (median survival time [MST]) of the patients who received post-treatment after sorafenib therapy and those who did not. Overall survival was significantly longer among the patients who received post-treatment after sorafenib therapy.

progression treatment after sorafenib therapy and of those who did not were 456 and 233 days, respectively, with those who underwent post-progression treatment exhibiting a better OS ($p < 0.001$) (Fig. 5).

Discussion

Sorafenib is a multitargeted tyrosine kinase inhibitor that suppresses tumor proliferation and angiogenesis. This agent carries a mild-to-moderate toxicity profile and exhibits antitumor activity against various solid tumors [17]. It was the first systemic agent that was proven to prolong the survival of patients with advanced HCC in two phase III trials [2, 18], and it is now the standard of care for systemically treated patients [5, 19–22]. The initial sorafenib dose recommended in the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial and the Asia-Pacific trial was 800 mg/day, but since sorafenib came into clinical use, there have been reports of lower initial doses. A large trial conducted among Japanese people, who have a smaller body surface area than Europeans and Americans, reported little dif-

ference between starting at 400 and 800 mg/day. In the roughly 7 years since sorafenib was approved in Japan, several studies have reported using other initial doses besides 800 mg.

Some have also reported administering sorafenib to patients other than those with Child-Pugh class A disease [23, 24]. In addition, better therapeutic results have been reported in patients who exhibited HFS, compared to those who did not [25, 26]. In the present study, in which we examined the outcomes of sorafenib administration in 314 patients at 5 general hospitals in Kagawa Prefecture, Japan, the results of the present study also showed comparable results.

In the present study, only about 10% of the patients started at an initial dose of 800 mg, but their median OS was 392 days, which is better than the results of the SHARP and Asia-Pacific trials. Regarding liver function at the start of treatment, about one-fourth of the patients had Child-Pugh class B disease. The good OS results achieved even against a background of poor liver function are thought to have been largely because administration had started at an optimal stage for some patients and because of the benefits of post-progression treatment after sorafenib therapy, as the importance of post-progression treatment after sorafenib has already been reported [27].

Moreover, methods of preventing and treating HFS have been established since sorafenib came into clinical use, so the results were likely less affected by dropouts due to HFS compared to when the drug was first approved. Previously, patients who exhibited HFS had better results than those who did not; a similar trend was observed in the present study.

Regarding liver function at the start of therapy, in the GIDEON (Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of Its Treatment with Sorafenib) trial the group of Child-Pugh class A patients had better OS than the group that started at Child-Pugh class B [28]; this was also observed in the present study. In the present study, even among the Child-Pugh class A patients, the group that started at class A-5 points had a significantly better OS than the group that started at class A-6 points; however, the OS of the group that started at class A-6 points was not significantly different from that of the Child-Pugh class B group. This suggests that among Child-Pugh class A patients, starting sorafenib when liver functions are well preserved, such as at class A-5 points, is preferable. The positive results observed in the present study for patients who underwent post-progression treatment such as TACE, hepatic arte-

rial infusion chemotherapy, or ablation [29–32] after sorafenib therapy also indicate that initiating therapy when liver function is well preserved (Child-Pugh class A-5 points) is beneficial.

Conclusion

The best results were observed when therapy was initiated at Child-Pugh class A-5 points, which indicates that it is preferable to start sorafenib at the time when liver function is still well preserved. Starting sorafenib at a reduced dose in Japanese patients is also thought to lead to

a better OS. Among the patients who exhibited HFS, those who were able to receive post-progression treatment after sorafenib therapy had good OS, which suggests that addressing this side effect is important for preserving the remaining hepatic reserve. The recent success of new systemic therapy agents [33, 34] and immunotherapies [35] will be expected to further improve survival among patients with advanced HCC.

Disclosure Statement

The authors have no conflicts of interest to declare.

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