Real-Life Clinical Practice with Sorafenib in Advanced Hepatocellular Carcinoma: A Single-Center Experience Second Analysis

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Significant factors contributing to the OS were treatment duration (p = 0.0204), up-to-7 criteria (p = 0.0400), increase of Child-Pugh score (p = 0.0008) and tumor response determined by the RECICL (p = 0.0007).

Conclusion: Based on the analysis, using many cases at a single center, we concluded that continuation of treatment with sorafenib for ≥90 days without decrease of liver function was critical if tumor response was determined as stable disease or higher.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world, and the incidence is increasing worldwide [1]. Because most patients are diagnosed with advanced disease stages, only 30% of patients receive potentially curative therapies, such as surgical resection [2–4], transplantation [5–8] or percutaneous ablation [9–13]. A majority of patients with unresectable HCC usually undergo palliative treatments, such as transarterial chemoembolization (TACE) [14–16], hepatic arterial infusion chemotherapy (HAIC) [17] and system-
Sorafenib is currently the standard systemic therapeutic agent approved for treatment of advanced HCC in patients with well-preserved liver function (Child-Pugh class A), within Barcelona Clinic Liver Cancer (BCLC) stage C, and showing progressive disease (PD) after locoregional therapy [17, 21–23]. Treatment using sorafenib is recommended based on the efficacy and safety reported by the 2 global randomized controlled trials: the Sorafenib HCC Assessment Randomized Protocol (SHARP) and the Asia-Pacific trials [24, 25]. The efficacy and safety of sorafenib in clinical practice have been addressed by additional field practice experiences, such as the Global Investigation of Therapeutic Decisions in HCC and of Its Treatment with Sorafenib (GIDEON) study [26, 27]. In Japan, sorafenib has been administered based on the consensus-based treatment algorithm for HCC proposed by the Japan Society of Hepatology [28]. Sorafenib is also recommended if TACE [14, 29, 30] and HAIC are not applicable but patients still carry a preserved liver function with Child-Pugh class A. In a previous study, we reported that the duration of administration was a significant prognostic factor for sorafenib treatment. A blood chemical test related to liver functions, such as serum levels of bilirubin as well as the tumor markers alpha-fetoprotein (AFP) and des-gamma carboxyprothrombin (DCP), could also be a marker predicting an overall survival (OS) [31–34]. In the current study, we retrospectively investigated 356 HCC patients treated with sorafenib at the Kinki University Hospital to elucidate the efficacy of sorafenib treatment and the clinical outcomes.

**Materials and Methods**

**Patients**

Between May 2009 and April 2015, 356 patients with HCC were treated with sorafenib at the Kinki University Hospital. Among these patients, 241 patients met the inclusion criteria listed below and were enrolled in the present study. The diagnosis of HCC was made by histological or radiologic findings using contrast-enhanced CT and/or dynamic MRI. Information regarding clinicopathological variables including demographic characteristics complete blood count, albumin, AFP, DCP, alanine aminotransferase (ALT), alkaline phosphatase (ALP), tumor stage (including number of focal lesions and maximum diameter of lesions in a contrast-enhancing disease), up-to-7 criteria and BCLC prognostic score were collected prior to treatment [35].

The inclusion criteria were as follows: (1) HCC diagnosed by histological examination or typical radiological findings (early enhancement followed by late washout on contrast-enhanced CT or dynamic MRI) and HCC refractory to radiofrequency ablation and TACE based on the indications for sorafenib, (2) Eastern Cooperative Oncology Group performance status of 0 or 1 and (3) Child-Pugh class A or B liver function. The exclusion criteria were as follows: (1) concomitant antineoplastic treatment and (2) TACE or radiofrequency ablation performed within 3 months of initiation of sorafenib. Our institution did not require informed consent for the review of patient records and images for a retrospective study, such as this was.

**Treatment Strategy Using Sorafenib**

Sorafenib was administered orally at a dose of 400 mg, twice daily. The initial dose was reduced by each attending physician according to the clinical conditions such as body weight, age, Eastern Cooperative Oncology Group performance status and liver function. Dose reduction and interruption of sorafenib were allowed and depended on the type and severity of adverse events (AEs). Dose reduction and discontinuation were determined based on the information in the package inserts. We continued sorafenib administration until the appearance of either intolerable toxicity or definitive progression of HCC. All AEs were graded according to the National Cancer Institute Common Terminology Criteria for AEs version 4.0 (CTCAE v4.0).

**Follow-Up**

Clinical and laboratory assessments and radiological evaluation were performed monthly and at 4- to 12-week intervals, respectively. Radiological assessment was blinded to the evolution of the disease and the patient outcomes. The patients who died before the first imaging assessment were classified as having experienced progression. OS was measured from the date of sorafenib initiation until the date of death.

**Response Evaluation Using the RECICL**

The Response Evaluation Criteria In Cancer of the Liver (RECICL) requires 2-directional measurement of tumors showing arterial enhancement. Complete response (CR) was defined as either a 100% tumor necrotizing effect or a 100% reduction in tumor size accompanied by disappearance of all contrast enhancements at any phase. Partial response (PR) was defined as either a 50% or greater reduction in tumor necrosis or size as determined by the 2-directional measurement. PD was defined as either a 50% or greater increase in tumor size or the appearance of one or more new lesions. The RECICL defined stable disease (SD) as the absence of either PR or PD; objective response rate as the percentage of CR + PR among all cases and disease control rate as the percentage of cases showing CR, PR or SD [36].

**Statistical Analysis**

Survival curves were calculated using the Kaplan–Meier method with the primary end point of death for analysis of OS. Patients who did not meet the end point were censored at the time of the last follow-up visit. Comparison of survival rates among the groups was estimated using the log-rank test, and comparison of categorical variables was performed using the $\chi^2$ test. For multiple comparisons, the Bonferroni correction was applied. A p value of <0.05 was considered statistically significant. All analyses were performed using the SAS statistical software version 8.2 (SAS Institute, Cary, N.C., USA), or the SPSS Medical Pack for Windows version 10.0 (SPSS, Inc., Chicago, Ill., USA).
Results

Baseline Characteristics

The baseline characteristics of the patients are summarized in Table 1. The patients, predominantly men (74.7%), had a median age of 73 years. Two hundred twenty-five patients (93.4%) were asymptomatic, with a PS of 0. One hundred twenty-one patients (50.2%) tested positive for the anti-hepatitis C virus antibody, 43 patients (17.8%) were positive for the hepatitis B virus surface antigen and 77 patients (32.0%) were negative for both. Sixty-four patients (26.6%) met the up-to-7 criteria [37]. The initial sorafenib dose in this study ranged from 200 to 800 mg/day. An initial dose of 800 mg/day was administered in 127 patients (52.7%).

After a month of treatment with sorafenib, 106 patients experienced a continuous or transient increase in the Child-Pugh score, while 82 patients showed no change and 24 patients showed a decrease in the Child-Pugh score by least 1 point. Twenty-nine patients were not evaluated. Prior treatment in the 203 cases included 60 resections, 116 local ablations, 164 cases of TACE, 34 cases of cytotoxic chemotherapy, 11 cases of radiation therapy and 29 cases of HAIC.

HCC Response to Sorafenib

The median OS of the entire cohort was 14.3 months (range 9.3–18.6 months). The 1- and 2-year survival rates were 52.5 and 34.6%, respectively (Fig. 1). The numbers of patients with CR, PR, SD and PD were 7, 34, 94 and 86, respectively. The objective response rate and disease control rate as estimated by the RECICL were 18.6 and 61.1%, re-

![Cumulative survival rate](image)

**Fig. 1.** OS of all patients treated with sorafenib. The Kaplan–Meier curves of the OS of the 241 patients who underwent treatment with sorafenib alone. Median survival time was 14.3 months (95% CI 9.3–18.6 months), and the 1- and 2-year survival rates were 52.5 and 34.6%, respectively.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases, n</th>
<th>%</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>Median (25–75%)</td>
<td>73 (66–77)*</td>
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<tr>
<td>Gender</td>
<td>Male</td>
<td>180</td>
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<tr>
<td></td>
<td>Female</td>
<td>61</td>
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<tr>
<td>ECOG PS</td>
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<td>225</td>
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<tr>
<td></td>
<td>1</td>
<td>16</td>
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<tr>
<td>Up-to-7 criteria</td>
<td>Within</td>
<td>64</td>
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<tr>
<td></td>
<td>Beyond</td>
<td>177</td>
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<tr>
<td>Virus status</td>
<td>Hepatitis B virus</td>
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<tr>
<td></td>
<td>Hepatitis C virus</td>
<td>121</td>
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<tr>
<td></td>
<td>Virus negative</td>
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<tr>
<td>BCLC stage</td>
<td>A</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>146</td>
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<tr>
<td>Initial dose of sorafenib, mg</td>
<td>200</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>400</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>800</td>
<td>127</td>
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<tr>
<td>Duration of sorafenib, days</td>
<td>Median (25–75%)</td>
<td>78 (28–239)*</td>
</tr>
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<td>Biochemical analysis, median (25–75%)</td>
<td>IU/l</td>
<td>33 (22–57)*</td>
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<td>Alkaline phosphatase, IU/l</td>
<td>405.4 (303–598.8)*</td>
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<td>White blood cell count, /μl</td>
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<td>Hemoglobin, g/dl</td>
<td>12.4 (11.1–13.5)*</td>
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<td></td>
<td>Platelet count, x10^9/μl</td>
<td>14.2 (9.5–20.5)*</td>
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<tr>
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<td>α-Fetoprotein, ng/dl</td>
<td>186 (14–4,243)*</td>
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<td>α-Fetoprotein L3, %</td>
<td>16.1 (0.6–49.3)*</td>
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<tr>
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<td>Des-γ carboxyprothrombin, mAU/dl</td>
<td>1,115.5 (78.5–9,884)*</td>
</tr>
</tbody>
</table>

* Dispersion variables are shown as median values (25–75%).
† Cases testing positive for hepatitis B virus surface antigen were regarded as cases of hepatitis B virus-related HCC and cases testing positive for hepatitis C antibody were regarded as cases of hepatitis C virus-related HCC.
spectively. Twenty patients were not evaluated. We compared the OS among the CR + PR, SD and PD groups using the Kaplan–Meier estimates. The comparisons of the survival curves showed that the median OS was 25.4 months (95% CI 17.9–53.4 months) in the CR + PR group, 18.8 months (95% CI 13.6–25.1 months) in the SD group and 7.3 months (95% CI 6.0–11.8 months) in the PD group (p < 0.001; fig. 2a). Pairwise comparisons verified a significantly longer OS in the CR + PR group than in the PD group (p < 0.001 by the log-rank test). Similarly, OS was significantly longer in the SD group than in the PD group (p = 0.001). In contrast, no significant differences in OS were detected between the CR + PR and SD groups (p = 0.392). We also compared the OS between the CR + PR + SD group and the PD group using the Kaplan–Meier estimates. The comparisons of the survival curves showed that the median OS was 20.7 months (95% CI 16.7–26.9 months) in the CR + PR + SD group and 7.3 months (95% CI 6.0–11.8 months) in the PD group (p < 0.001; fig. 2b).

**Prognostic Factors of HCC Patients Treated with Sorafenib**

We analyzed the baseline patient characteristics to identify factors that affected OS after sorafenib therapy. Univariate analysis revealed statistically significant differences in OS for the following variables: treatment duration (p < 0.0001), up-to-7 criteria (p < 0.0001), portal invasion (p < 0.0001), extrahepatic spread (p = 0.0018), PS (p = 0.0113), albumin (p = 0.0004), total bilirubin (p < 0.0001), white blood cell count (p = 0.0172), platelet count (p = 0.0335), ALT (p = 0.0136), ALP (p < 0.0001), DCP (p < 0.0001), AFP-L3 (p = 0.0131), BCLC stage (p = 0.0006), Child-Pugh score increase (p < 0.0001) and response evaluation using the RECICL (p < 0.0001) at the initiation of sorafenib therapy (table 2). Multivariate analysis revealed statistically significant differences in OS for the following variables: treatment duration (p = 0.0204), up-to-7 criteria (p = 0.0400), Child-Pugh score increase (p = 0.0008) and response evaluation using the RECICL (p = 0.0007; table 3).

**Drug-Related AEs of Sorafenib**

The overall incidence of drug-related AEs of any grade was 77.3% (187 of 241 patients) in our cohort (table 4). The most frequently reported drug-related AEs in patients treated with sorafenib were hand-foot skin reaction (109, 45.0%), diarrhea (76, 31.4%), hypertension (61, 25.2%), abnormal liver function (32, 13.2%), anorexia...

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Fig. 2. The Kaplan–Meier curves of OS based on response to treatment as estimated by the RECICL. The Kaplan–Meier curves of the OS of the 221 patients based on response to sorafenib therapy as estimated by the RECICL. a The median OS of the patients classified as CR + PR, SD and PD, respectively, was 25.4, 18.8 and 7.3 months by the RECICL (p < 0.0001 by log-rank test). b The median OS of the patients classified as CR + PR + SD and PD, respectively, was 20.7 and 7.3 months by the RECICL (p < 0.0001 by log-rank test).
Aloe vera (31, 12.8%), alopecia (11, 4.5%) and hoarseness (10, 4.1%). AEs of Grade 3 or more as defined by CTCAE v4.0 were observed in 23.6% (57 patients) of patients in our cohort: hand-foot skin reaction (28, 11.6%), liver dysfunction (12, 5.0%), hypertension (9, 3.7%), diarrhea (4, 1.7%), erythema multiforme (4, 1.7%), decreased platelet count (3, 1.2%), anorexia (2, 0.8%) and anemia (1, 0.4%).

Discussion

Since the demonstration of the efficacy of the molecular targeted agent sorafenib in the SHARP and the Asia-Pacific trials, various studies have reported on the efficacy of this drug. It has been 6 years since the approval of sorafenib in Japan. In the current study, we comprehen-
sively analyzed the clinical course of all patients treated with sorafenib at our hospital and reported the treatment outcomes as well as the factors contributing to OS as a single-center experience.

The OS following sorafenib treatment was 14.3 months at our hospital, which was longer than that reported in the SHARP and the Asia-Pacific trials. The sorafenib-induced AEs of any grade were 77.3%, and Grade 3 or higher events accounted for 23.6%, demonstrating that AE outcomes were not greatly different from those of the SHARP and the Asia-Pacific trials [24, 25]. Furthermore, no remarkable difference was observed in comparison to the sorafenib-induced AEs reported in the GIDEON [27].

Our outcomes regarding AEs did not show great differences in comparison to other reports [38, 39], but the survival outcome in our study was superior to that of the SHARP and the Asia-Pacific trials [24, 25].

Currently, sorafenib is recommended for cases unresponsive to TACE [29]. TACE is considered to be effective for local control of the tumor. However, the multiple procedure of TACE should lead to deterioration of liver function where treatment with sorafenib could not be applicable; such a condition would result in the decrease of OS in HCC patients. Therefore, if the patient showed a poor tumor response to TACE, sorafenib treatment is strongly recommended instead of continuing TACE even if the patient is still in an early stage. The relatively early induction of sorafenib for patients who did not respond to TACE could be a cause of longer survival in our study as compared to other studies.

The results of this study showed that factors contributing to survival include the administration period of sorafenib, up-to-7 criteria, change in Child-Pugh score and response evaluation. Sorafenib could induce several antitumor effects, including tumor necrosis; the increase of OS, which is the most important outcome of sorafenib treatment, should be attributed to the inhibition of tumor proliferation [40]. Therefore, long-term administration with control AE should be critical to extract the potential of sorafenib even in cases with SD. Furthermore, as the decrease in the Child-Pugh score results in the decrease in OS, the preservation of liver function is also important in addition to the control of AEs. As there is a report claiming that branched chain amino acid preparations are effective in preventing decreases in the albumin levels during sorafenib administration [41], it is also necessary to take a supportive therapy to preserve liver function.

Based on our experience with a large number of cases, we conclude that contentious treatment with sorafenib for a long period is critical to extract the maximum efficacy even if SD or a more favorable outcome is obtained, because sorafenib is the only molecular targeted drug that has demonstrated efficacy for advanced HCC, and there is no second-line therapy with sorafenib.

Disclosure Statement

Authors declare no conflict of interest.

References