pISSN 1598-2998, eISSN 2005-9256

Cancer Res Treat. 2016;48(4):1243-1252

http://dx.doi.org/10.4143/crt.2015.278

Original Article

Open Access

Real-Life Experience of Sorafenib Treatment for Hepatocellular Carcinoma in Korea: From GIDEON Data

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Received July 26, 2015
Accepted February 15, 2016
Published Online February 24, 2016

Purpose

The purpose of this study is to report real life experiences of sorafenib therapy for hepatocellular carcinoma (HCC) in Korea, using a subset of data from GIDEON (Global Investigation of Therapeutic Decisions in HCC and of Its Treatment with Sorafenib; a large, prospective, observational study).

Materials and Methods

Between January 2009 and April 2012, a total of 497 patients were enrolled from 11 sites in Korea. Of these, 482 patients were evaluable for safety analyses. Case report forms of paper or electronic version were used to record safety and efficacy data from all patients.

Results

More patients of Child-Pugh A received sorafenib for > 8 weeks than did patients of Child-Pugh B (55.5% vs. 34.3%). Child-Pugh score did not appear to influence the starting dose of sorafenib, and approximately 70% of patients both in Child-Pugh A and B groups received the recommended initial daily dose of 800 mg (69.0% and 69.5%, respectively). The median overall survival (OS) and time to progression (TTP) were 8.5 months and 2.5 months. In Child-Pugh A patients, the median OS and TTP were 10.2 months and 2.5 months. The most frequent treatment-emergent drug-related adverse event was hand-foot skin reaction (31.7%), followed by diarrhea (18.0%). The incidence of treatment-emergent adverse events was similar in both Child-Pugh A (85.4%) and Child-Pugh B (84.8%) patients.

Conclusion

Sorafenib was well tolerated by Korean HCC patients in clinical settings, and the safety profile did not appear to differ by Child-Pugh status. Survival benefit in Korean patients was in line with that of a previous pivotal phase III trial (SHARP).

Key words
Hepatocellular carcinoma, Sorafenib, Korea

Introduction

Hepatocellular carcinoma (HCC) represents the fifth most common cancer worldwide and is known to cause significant public health problems, particularly in association with chronic hepatitis B (CHB) or chronic hepatitis C [1]. Based on available data, more than half of HCC cases and deaths are estimated to occur in North Eastern Asian areas including Korea, China, Taiwan, and Japan where viral hepatitis B or C is highly prevalent [2]. Unlike other solid tumors, HCC presents several unique characteristics, including multifocal tumorigenesis, frequent vascular invasion, recurrence, and most importantly associated cirrhotic background, altogether making a HCC hard to cure malignancy. In addition, HCC is characterized by heterogeneity in terms of genetic diversity, tumor behavior, and patient population [3,4].

In spite of an effort to detect early stage of HCC in patients

at risk through a surveillance program, a substantial proportion of patients with HCC are still diagnosed at an advanced stage of the disease when the survival rate is poor [5]. Potentially curative treatments including resection, ablation, and liver transplantation can be applied only to HCC detected at an early stage (single nodule ≤ 5 cm or 2-3 nodules ≤ 3 cm) [6]. Transarterial chemoembolization (TACE) is regarded as standard-of-care for multinodular HCC without vascular invasion and extrahepatic metastasis [7].

Sorafenib is the first developed molecular targeted agent in HCC which blocks the Raf/MEK/ERK pathway by inhibiting Raf serine/threonine kinase and also inhibiting the upstream receptor tyrosine kinases that are important in angiogenesis, such as vascular endothelial growth factor receptor (VEGFR)-2, VEGFR-3, platelet derived growth factor receptor β and kit [8]. In a global phase III, randomized trial of 602 patients with advanced HCC, the median overall survival (OS) was 10.7 months in the sorafenib group compared with 7.9 months in the placebo group (hazard ratio, 0.69; 95% confidence interval, 0.55 to 0.87; $p < 0.001$). The survival benefit was preceded by a delay in time to progression (TTP): 5.5 months for sorafenib versus 2.8 months for control ($p < 0.001$) [9]. Another phase III trial conducted in the Asia-Pacific (AP) area confirmed the survival benefit of sorafenib in unresectable HCC [10]. Based on these results, sorafenib was approved as the first systemic drug for patients with advanced HCC not amenable to resection, transplantation, or locoregional treatments [7,8].

Data obtained from well-controlled clinical trials might not be translated into a real-clinical setting, particularly in HCC treatment. The efficacy and safety of sorafenib in HCC patients with liver dysfunction remain largely unknown, as only patients of Child-Pugh A were included in the trials. GIDEON (Global Investigation of Therapeutic Decisions in HCC and of Its Treatment with Sorafenib) is a prospective, non-interventional study conducted to fulfil post-approval commitments to licensing agencies [11]. GIDEON is one of the largest studies conducted in patients with unresectable HCC, and the data facilitate broad evaluation of patient subgroups. Many subanalyses were therefore planned and performed, with a focus on potentially predictive or prognostic factors, including Child-Pugh score, Barcelona Clinic Liver Cancer (BCLC) stage, and etiology.

Herein, we report on real-life experience of sorafenib therapy for HCC in Korea, using a subset of the GIDEON data.

Materials and Methods

1. The design and objectives of GIDEON

GIDEON recruited patients who were candidates for systemic therapy, for whom the decision to treat with sorafenib was made in real-life practice conditions including patients with Child-Pugh B liver function. The details of the study design have been previously published [12]. The primary objective of GIDEON is to evaluate the safety of sorafenib in patients with unresectable HCC in real-life. The secondary objectives are to explore drug efficacy in terms of OS, progression-free survival, TTP, response rate (RR), and disease control rate (DCR); to determine the duration of therapy according to various patient characteristics; to assess methods of patient evaluation, diagnosis, and follow-up; to assess comorbidities and their influence on treatment and outcome in real-life practice rather than a controlled clinical trial setting; and to evaluate the practice pattern of the physicians involved in the care of these patients.

2. Patients

Eligible patients were those diagnosed histologically or radiographically with HCC, who have a life expectancy of > 8 weeks and in whom the decision to treat with sorafenib was made by their physician. Detailed inclusion criteria are outlined in the previously published study design report [11]. Exclusion criteria were those dictated by the manufacturer of the drug. Written informed consents were given by all patients and the study was approved by the individual institutional review board. More than 3,000 patients were recruited from 39 countries of five geographic regions between January 2009 and April 2012. A total of 497 patients were enrolled from 11 sites in Korea during the same period. Of these, 482 patients were evaluable for safety analyses after exclusion of 15 patients who did not receive at least one dose of sorafenib during the study period (n=5) or did not undergo at least one assessment for follow-up after initiating study medication, regardless of previous systemic treatment (n=10).

3. Data collection and analyses

Paper or electronic case report forms were used to record data from all enrolled patients at study entry and start of sorafenib, then at intervals chosen by the prescribing physician until death, withdrawal from the study, or loss to follow-up. All adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria ver. 3.0 (National Cancer Institute, Bethesda, MD), and their

likely relationship to sorafenib therapy was documented. HCC assessment was made by computed tomography or other equivalent radiographical method and was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST). All efficacy and safety data were summarized using descriptive statistics.

Results

1. Baseline patient characteristics

The baseline demographic and tumor characteristics of 482 patients evaluable in terms of safety analysis are shown in Table 1. Male patients predominated (85.5%), and 76.8% of patients were under 65 years of age (median age, 55.0 years). The most common underlying etiology was hepatitis B virus (HBV) infection (81.1%), followed by alcohol use (26.3%). Most patients were Child-Pugh A class (56.8%), with fewer Child-Pugh B patients (21.8%). Eastern Cooperative Oncology Group (ECOG) performance status was 1 (44.8%) and 0 (33.8%) in most patients.

All BCLC stages were represented but most patients (60.8%) were BCLC stage C, while 4.8% of patients were BCLC stage B, 4.6% stage D, and 0.8% stage A. In terms of TNM staging, stage III and IV patients accounted for 25.9% and 52.5% of all patients, respectively, and only a few were TNM stage I (0.2%) or II (1.9%). Portal vein thrombosis was observed in 50.4% of patients and extrahepatic spread in 66.0%. Prior locoregional treatment (LRT) was administered in 68.3% of all patients, with TACE being the most common. Thus, 60.6% of all patients had undergone prior TACE compared with 14.5%, 8.3%, and 2.1% of patients treated with prior radiofrequency ablation, hepatic arterial infusional chemotherapy, or percutaneous ethanol injection, respectively.

2. Sorafenib administration

Data on sorafenib administration are shown in Table 2. The mean duration of treatment was 15 weeks (median, 8.7 weeks). Approximately 67% of patients received the approved initial daily dose of 800 mg, while 31.5% received a half dose (400 mg). Only a few patients received 200 mg or 600 mg as an initial daily dose (0.6% and 0.8%, respectively). Patients were most frequently treated for 4-8 weeks (22.0%), followed by ≤ 4 weeks (21.4%) and > 28 weeks (12.7%).

Analysis of sorafenib dosing was based on Child-Pugh class (A or B) (Table 2). The duration of sorafenib administration was generally longer in Child-Pugh A than B patients.

Table 1. Baseline patient characteristics

Variable	No. (%) (n=482)
Age (yr)	
Mean±SD	55.9±10.5
Median	55.0
< 65	370 (76.8)
65 to < 75	95 (19.7)
≥ 75	17 (3.5)
Sex	
Male	412 (85.5)
Female	70 (14.5)
Etiology of HCC[a]	
HBV	391 (81.1)
HCV	26 (5.4)
Alcohol	127 (26.3)
Unknown	22 (4.6)
Cirrhosis	
Yes	307 (63.7)
No	101 (21.0)
Unknown	74 (15.4)
Child-Pugh class	
A	274 (56.8)
B	105 (21.8)
C	6 (1.2)
Unknown	97 (20.1)
BCLC stage	
A	4 (0.8)
B	23 (4.8)
C	293 (60.8)
D	22 (4.6)
Unknown	140 (29.0)
TNM stage	
I	1 (0.2)
II	9 (1.9)
IIIa	72 (14.9)
IIIb	19 (3.9)
IIIc	34 (7.1)
IV	253 (52.5)
Unknown	94 (19.5)
Portal vein thrombosis	243 (50.4)
Extrahepatic spread	318 (66.0)
ECOG at start of therapy	
0	163 (33.8)
1	216 (44.8)
≥ 2	36 (7.5)
Unknown	37 (13.9)
Prior anti-cancer therapy	
LRT	329 (68.3)
TACE	292 (60.6)
RFA	70 (14.5)
HAIC	40 (8.3)
PEI	10 (2.1)

SD, standard deviation; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; LRT, locoregional therapy; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; HAIC, hepatic arterial infusion chemotherapy; PEI, percutaneous ethanol injection. [a]Multiple responses were possible for etiology of underlying disease and LRT.

Table 2. Sorafenib administration according to Child-Pugh class

Variable	Total (n=482)	Child-Pugh A (n=274)	Child-Pugh B (n=105)
Duration of treatment (wk)			
Mean±SD	14.93±17.36	17.01±19.73	8.55±8.66
Median	8.70	10.05	6.00
≤ 4	103 (21.4)	47 (17.2)	35 (33.3)
4-8	106 (22.0)	65 (23.7)	24 (22.9)
8-12	67 (13.9)	37 (13.5)	14 (13.3)
12-16	42 (8.7)	27 (9.9)	8 (7.6)
16-20	36 (7.5)	20 (7.3)	6 (5.7)
20-24	22 (4.6)	16 (5.8)	1 (1.0)
24-28	19 (3.9)	10 (3.6)	3 (2.9)
> 28	61 (12.7)	42 (15.3)	4 (3.8)
Unknown	26 (5.4)	10 (3.6)	10 (9.5)
Average daily dose (mg)			
Mean±SD	626.0±177.0	626.8±173.0	640.3±178.2
Median	669.5	661.5	715.0
Unknown (n)	52	26	13
Initial dose (mg)			
200	3 (0.6)	1 (0.4)	1 (1.0)
400	152 (31.5)	83 (30.3)	29 (27.6)
600	4 (0.8)	1 (0.4)	2 (1.9)
800	323 (67.0)	189 (69.0)	73 (69.5)
Permanent discontinuation of sorafenib due to AE	127 (26.3)	81 (29.6)	34 (32.4)

Values are presented as number (%) unless otherwise indicated. Data for patients with not evaluable Child-Pugh status (n=97) and Child-Pugh C (n=6) is not included in this table. SD, standard deviation; AE, adverse event.

More Child-Pugh A patients received sorafenib for > 8 weeks compared with Child-Pugh B patients (55.5% vs. 34.3%). However, some Child-Pugh B patients were treated for longer periods, and 3.8% of Child-Pugh B patients received > 28 weeks of sorafenib therapy. Child-Pugh score did not appear to influence the starting dose of sorafenib; approximately 70% of patients in both Child-Pugh A and B class received the recommended initial daily dose of 800 mg (69.0% and 69.5%, respectively) and the median daily dose was slightly lower in Child-Pugh A patients than B patients (661.5 mg vs. 715.0 mg). The frequency of permanent discontinuation of sorafenib due to AEs was similar between Child-Pugh A and B patients (29.6% and 32.4%, respectively).

3. Response to sorafenib and treatment outcomes

Response to sorafenib was assessed using intent-to-treat analysis (ITT) of all patients who received at least one dose of sorafenib. A total of 490 patients were valid for the ITT set. According to RECIST criteria, three patients (0.61%) achieved complete response (CR), while partial response (PR) and stable disease (SD) were observed in 10 (2.04%) and 131 (26.73%) patients. There were 247 (50.41%) patients who showed progressive disease (Table 3). The objective RR (CR+PR) was 2.65% and the DCR, defined as proportion of patients with the best response rating of documented CR, PR, or SD maintained for at least 28 days from the first demonstration of that rating, was 79 (16.12%). Of 13 patients who achieved an objective response, the median time to response was 65 days and the median duration of response was 556 days. The median duration of SD was 68 days.

The median OS and TTP were 8.5 months and 2.5 months, respectively (Fig. 1). In particular, the median OS and TTP in Child-Pugh A patients was 10.2 months and 2.5 months. Of note, the OS and TTP appeared to be longer in patients whose starting dose was 800 mg rather than 400 mg. The OS and TTP were 9.3 and 2.8 months in patients with a starting dose of 800 mg, compared to 7.8 and 2.4 months in those with 400 mg, respectively (Table 4).

4. Safety assessments

At least one treatment-emergent adverse event (TEAE) was reported for 82.2% of patients (Table 5), and 293 patients

Table 3. Response to sorafenib by intent-to-treat analysis

Response	No. (n=490)	Rate (%)	90% CI (%)
Complete response	3	0.61	0.17-1.57
Partial response	10	2.04	1.11-3.44
Stable disease[a)]	131	26.73	23.45-30.22
Progressive disease	247	50.41	46.60-54.22
Not assessable	99	20.20	17.26-23.42
Objective response	13	2.65	1.58-4.19
Disease control rate[b)]	79	16.12	13.45-19.11

Tumor response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.0. Denominator for rates (%) and 90% confidence interval (CI) were based on patient population for analysis. [a)]Stable disease: patients with best overall response of stable disease at least 6 weeks after first dose of sorafenib, [b)]Disease control rate: patients with best response rating of documented complete response, partial response, or stable disease maintained for at least 28 days from the first demonstration of that rating.

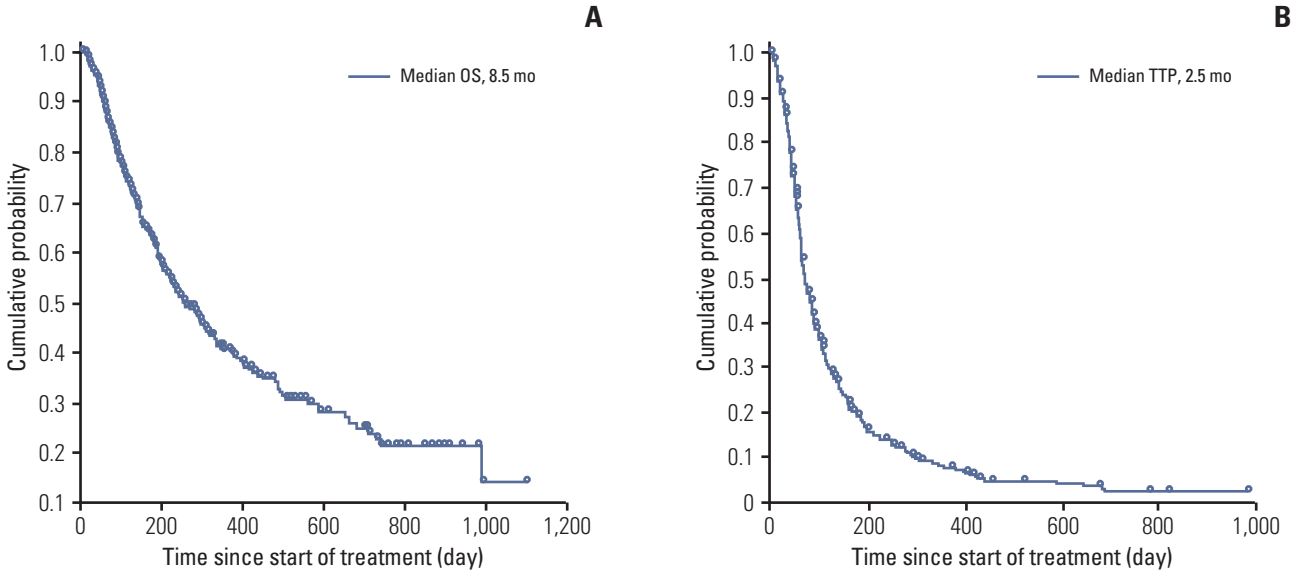

Fig. 1. The median overall survival (OS) (A) and time to progression (TTP) (B) in the entire study population was 8.5 months and 2.5 months, respectively. The response was estimated based on Response Evaluation Criteria in Solid Tumors ver. 1.0.

(60.8%) experienced drug-related TEAEs. Of these, 16.2% patients had grade 3 events and 0.8% of patients had grade 4 events. Overall, 36.9% of patients (n=178) experienced treatment-emergent serious adverse events (SAEs) and 4.4% experienced treatment-emergent drug-related SAEs. Sorafenib was permanently discontinued as a result of TEAEs in 26.3% of patients.

The incidence of TEAEs was similar between Child-Pugh A (85.4%) and Child-Pugh B (84.8%) patients (Table 5). However, the incidence of drug-related TEAEs and that of grade 3 TEAEs was higher in Child-Pugh A than B patients (treatment-emergent drug-related AEs, 66.4% vs. 56.2%; grade 3 TEAEs, 28.5% vs. 18.1%). Treatment-emergent SAEs occurred more often in Child-Pugh B than A patients (52.4% vs. 34.3%). Treatment-emergent drug-related SAEs occurred in 4.4% of Child-Pugh A and 7.6% of Child-Pugh B patients. The rates of sorafenib discontinuation due to AEs, regardless of any causal relationship with sorafenib, was similar in Child-Pugh A (29.6%) and B patients (32.4%). Treatment emergent deaths were higher in Child-Pugh B than A patients (28.6% vs. 10.9%).

The most commonly reported TEAEs in the overall popu-

Table 4. Overall survival and time to progression according to the starting dose of sorafenib

Sorafenib	No.	Median OS (mo)	95% CI (mo)	Median TTP (mo)	95% CI (mo)
400 mg	154	7.8	5.7-10.9	2.4	2.0-3.0
800 mg	329	9.3	7.3-12.5	2.8	2.2-3.2

OS, overall survival; CI, confidence interval; TTP, time to progression.

Table 5. Overview of safety data by Child-Pugh score

Adverse event summary	Total (n=482)	Child-Pugh A (n=274)	Child-Pugh B (n=105)	Child-Pugh C (n=6)	Not evaluable (n=97)
TEAE (all grades)	396 (82.2)	234 (85.4)	89 (84.8)	4 (66.7)	69 (71.1)
Treatment-emergent drug-related AE (all grades)	293 (60.8)	182 (66.4)	59 (56.2)	1 (16.7)	51 (52.6)
Treatment-emergent SAE (all grades)	178 (36.9)	94 (34.3)	55 (52.4)	4 (66.7)	25 (25.8)
Treatment-emergent drug-related SAE (all grades)	21 (4.4)	12 (4.4)	8 (7.6)	0	1 (1.0)
TEAE resulting in permanent discontinuation of sorafenib	127 (26.3)	81 (29.6)	34 (32.4)	1 (16.7)	11 (11.3)
All TEAE with CTCAE grade 3	120 (24.9)	78 (28.5)	19 (18.1)	0	23 (23.7)
All treatment-emergent drug-related AE with CTCAE grade 3	78 (16.2)	49 (17.9)	14 (13.3)	0	15 (15.5)
All TEAE with CTCAE grade 4	24 (5.0)	10 (3.6)	8 (7.6)	0	6 (6.2)
All treatment-emergent drug-related AE with CTCAE grade 4	4 (0.8)	3 (1.1)	0	0	1 (1.0)

Values are presented as number (%). Adverse event (AE) was assessed by National Cancer Institute Common Toxicity Criteria (NCI CTC) ver. 3.0 and worst grade. A serious adverse event (SAE) is defined as any AE occurring at any dose that results in any of the following outcomes: death; life-threatening; hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity; congenital anomaly/birth defect; medically important event. TEAE, treatment-emergent adverse event; CTCAE, Common Terminology Criteria for Adverse Events.

lation included hand-foot skin reaction (32.2%), diarrhea (22.8%), and abdominal pain (20.1%) (Table 6). Hand-foot skin reaction (6.0%), bilirubin elevation (5.2%), and thrombocytopenia (4.5%) were the most commonly reported grade 3 or 4 AEs in Korea, while the most common grade 4 AEs were liver dysfunction (1.2%) and bilirubin elevation (0.8%). The most frequent treatment-emergent drug-related AE was hand-foot skin reaction (31.7%), followed by diarrhea (18.0%), rash/desquamation (9.3%), and anorexia (8.1%). The safety profile of Child-Pugh B patients was generally consistent with the overall safety profile.

Discussion

GIDEON is the largest, prospective, non-interventional global study to investigate the treatment of patients with unresectable HCC in the real world, and reflects the current practice of participating physicians [12].

Looking at the final global data, a total of 3,371 patients were enrolled from 39 countries across five different regions and data on 3,202 patients were available for safety analysis [13]. In terms of etiology, the frequency of HBV infection was similar to that of hepatitis C virus infection globally (36.5% vs. 32.9%). Of all patients, 52% were BCLC stage C, while 20% of patients had BCLC-B. Regarding Child-Pugh class, sorafenib was prescribed in 20.8% of Child-Pugh B patients, indicating the real-life pattern of sorafenib use in treatment

Table 6. Incidences of treatment-emergent and treatment-emergent drug-related adverse events (AE)

AE[a)]	Treatment-emergent AEs		Treatment-emergent drug-related AEs	
	Total (n=482)	Grade 3 or 4 (n=482)	Total (n=482)	Grade 3 or 4 (n=482)
Any AE	396 (82.2)	144 (29.9)	293 (60.8)	82 (17.0)
Blood/bone marrow	56 (11.6)	36 (7.4)	40 (8.3)	22 (4.6)
Thrombocytopenia	34 (7.1)	22 (4.5)	27 (5.6)	15 (3.1)
Constitutional symptoms	110 (22.8)	9 (1.9)	37 (7.7)	2 (0.4)
Fatigue	50 (10.4)	4 (0.8)	28 (5.8)	2 (0.4)
Fever	41 (8.5)	1 (0.2)	7 (1.5)	-
Dermatology/Skin	202 (41.9)	36 (7.5)	190 (39.4)	34 (7.1)
Alopecia	32 (6.6)	-	31 (6.4)	-
Hand-foot skin reaction	155 (32.2)	29 (6.0)	153 (31.7)	29 (6.0)
Rash/Desquamation	53 (11.0)	5 (1.0)	45 (9.3)	5 (1.0)
Gastrointestinal	236 (49.0)	46 (9.5)	153 (31.7)	16 (3.3)
Anorexia	69 (14.3)	8 (1.7)	39 (8.1)	3 (0.6)
Ascites	40 (8.3)	18 (3.7)	-	-
Constipation	24 (5.0)	-	6 (1.2)	-
Diarrhea	110 (22.8)	10 (2.1)	87 (18.0)	9 (1.9)
Distension	25 (5.2)	3 (0.6)	1 (0.2)	-
Heartburn	29 (6.0)	-	15 (3.1)	-
Mucositis in oral cavity	25 (5.2)	1 (0.2)	19 (3.9)	1 (0.2)
Nausea	56 (11.6)	2 (0.4)	30 (6.2)	1 (0.2)
Vomiting	29 (6.0)	1 (0.2)	15 (3.1)	1 (0.2)
Hemorrhage/Bleeding	63 (13.1)	21 (4.3)	19 (3.9)	2 (0.4)
Hepatobiliary/Pancreas	53 (11.0)	16 (3.4)	4 (0.8)	2 (0.4)
Liver dysfunction	40 (8.3)	9 (1.8)	4 (0.8)	2 (0.4)
Infection	32 (6.6)	11 (2.3)	3 (0.6)	1 (0.2)
Lymphatics (edema)	26 (5.4)	1 (0.2)	2 (0.4)	-
Metabolic/Laboratory	68 (14.1)	49 (10.2)	10 (2.1)	7 (1.4)
Bilirubin elevation	36 (7.5)	25 (5.2)	2 (0.4)	2 (0.4)
Neurology	60 (12.4)	18 (3.7)	14 (2.9)	1 (0.2)
Encephalopathy	26 (5.4)	13 (2.7)	3 (0.6)	1 (0.2)
Pain	161 (33.4)	31 (6.4)	-	37 (7.7)
Abdominal pain	97 (20.1)	18 (3.7)	-	17 (3.5)
Pulmonary/Upper respiratory	80 (16.6)	9 (1.9)	-	12 (2.5)
Cough	26 (5.4)	-	-	-
Dyspnea	31 (6.4)	8 (1.7)	-	1 (0.2)

Values are presented as number (%). [a)]Assessed by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) ver. 3.0.

of HCC. One-third of all patients had portal vein thrombosis. The proportion of patients having undergone previous LRT was 57.5%. In Korean data (total, 482 patients), the most common cause of HCC was HBV infection (81.1%). The frequency of advanced stage (BCLC-C) (60.8%) tended to be higher than the global figure, but the proportion of patients with decreased liver function (Child-Pugh B) (21.8%) was similar to the global proportion, although unknown was 20.1%. Portal vein thrombosis was more common in Korea (50.4%), and more patients had been previously treated with locoregional therapy (68.3%), and 66% of patients had extrahepatic spread.

Overall, Korean patients treated with sorafenib had more advanced diseases and more unfavorable prognosis than patients from other countries.

The drug safety profile was consistent with both those of previously published phase III trials and the final GIDEON data (Table 5) [9,10,13]; the most common drug-related AEs were hand foot skin reaction (31.7%) and diarrhea (18%). Collectively, the incidence of AEs including SAEs and treat-

Table 7. Survival benefit of sorafenib in studies

Variable	GIDEON global data (n=3,202)	GIDEON Korean data (n=482)	SHARP (n=299)	AP (n=150)
Child-Pugh A	1,968 (61.5)	279 (56.8)	284 (95)	146 (97.3)
Survival (overall, mo)	10.8	8.5	10.7	6.5
Child-Pugh A	13.6	10.2	-	-
Time to progression (overall, mo)	4.8[a)]	2.5[a)]	5.5[b)]	2.8[b)]
Child-Pugh A	4.7[a)]	2.5[a)]	-	-

Values are presented as number (%). GIDEON, Global Investigation of Therapeutic Decisions in hepatocellular carcinoma and of Its Treatment with Sorafenib; AP, Asian-Pacific. [a)]Assessed by Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.0, [b)]Assessed by RECIST.

ment-emergent AEs was similar in Child-Pugh A and B patients, and in particular, Child-Pugh B did not appear to increase drug-related AEs or the rate of permanent sorafenib discontinuation, compared to Child-Pugh A (Table 4). A possible explanation for this is the consistent pharmacokinetics (PK) of sorafenib in Child-Pugh A and B patients. The PK data indicate that the maximal concentration and the geometric means of area under curve at steady state were not significantly different between Child-Pugh A and B patients. This characteristic of PK might make Child-Pugh score less influential on the safety of sorafenib treatment [14].

Although a non-interventional study cannot thoroughly evaluate drug efficacy, and data interpretation must be done with caution, we sought to determine the efficacy of sorafenib in Korean HCC patients in a real life practice setting. The median OS was 8.5 months, and thus seems superior to that observed in the AP phase III study, even though more BCLC-B patients were included in GIDEON (11.2% vs. 4.7%) [10]. However, we also have to consider that the majority of patients in the AP study were of Child-Pugh A. If only Child-Pugh A patients are considered, the median OS is 13.6 and 10.2 months in global and Korean data, respectively, and these are superior to the AP study and seem comparable even to SHARP (10.7 months). In addition, the median TTP was 2.5 months in Korean patients with Child-Pugh A, also comparable to that of the AP trial (Table 7). Consequently, our result has confirmed the benefit of sorafenib in Korean patients with HCC, showing longer OS compared to the AP sorafenib study. Another finding from this study was the comparison of efficacy between different starting dose of sorafenib (reduced vs. full). Due to various reasons including concern of AE and old patient's age, starting dose of sorafenib is occasionally reduced to half (400 mg) or to three-fourths (600 mg). Despite several selection biases regarding comparison of efficacy between different starting doses and no analytical statistics were performed, OS in patients who received 800 mg appeared to be longer (median survival, 9.3 months) than that of patients on 400 mg (7.8 months). Such a result is in agreement with that from the global GIDEON trial [15]. However, further studies are necessary to clarify whether a full dose of sorafenib can result in longer survival or better baseline patient characteristics, leading physicians to start and maintain full dose of sorafenib.

Overall, the survival benefit in the Korean GIDEON study was less than that observed globally (median OS, 10.8 months globally vs. 8.5 months in Korea), probably because Korean patients presented with more advanced disease represented by high frequency of BCLC-C, Child-Pugh B, and involvement of portal vein as well as predominant etiology of CHB.

Several international guidelines suggest the use of sorafenib in treatment of Child-Pugh B patients with advanced HCC, although most enrolled patients in randomized trials were Child-Pugh A; such patients have no other treatment option because of poor liver function [8,16]. Sorafenib has been used in treatment of Child-Pugh B patients in Korea, and was prescribed for 21.8% of all patients. The initial dose and average daily dose in Child-Pugh B patients were similar to those administered to Child-Pugh A patients, and the extent of permanent treatment discontinuation triggered by development of AEs was similar in both groups. Although treatment duration tended to be shorter in Child-Pugh B patients, the most common reason for treatment discontinuation except disease progression was patient's own decision including financial reason. AE was the second most common reason; however, the incidence is not different between Child-Pugh A and B. In addition, neither the safety profile nor the incidence of AEs differed between Child-Pugh A and B patients. Accordingly, Child-Pugh score did not influence sorafenib dosing strategy and we found no evidence that AEs associated with sorafenib were more prevalent in patients with decreased liver function. Nevertheless, more prospective evidence is needed in terms of effectiveness and safety of sorafenib treatment in advanced HCC with Child-Pugh B. The interpretation of finding that the safety profile of sorafenib by the

starting dose (800 mg vs. 400 mg) was not significantly different between the two groups in our study also requires caution because baseline patients' characteristics might not be similar (data not shown).

The GIDEON study is an observational study and this result is limited in data analysis due to several reasons including no control arm, selection bias, and limited data input from investigators. In particular, the economic issue of sorafenib due to non-reimbursement may affect the results regarding the cause of its discontinuation, but also the duration of therapy within this study. However, a non-interventional study can provide an opportunity to observe real clinical practice enabling the assessment of a wider patient population and this result also clearly showed the treatment pattern as well as the safety and efficacy of sorafenib in Korean HCC patients.

Conclusion

In conclusion, our study subanalyzed the Korean data from the GIDEON study and is the first, largest and prospective report on real clinical practice of sorafenib for HCC treatment in Korea. The overall results were in agreement with final data of the GIDEON study. Sorafenib was well tolerated by Korean HCC patients in real-life settings, and the drug safety profile did not appear to vary by Child-Pugh status, which also did not appear to influence the approach to sorafenib dosing, although the treatment duration was shorter in Child-Pugh B than A patients. The survival benefit of sorafenib in Korean HCC patients seems less than global data as Korean patients were in more advanced diseases. Nevertheless, the observed efficacy of sorafenib in Korean HCC patients was consistent with that observed in earlier randomized trials (SHARP or AP) despite inclusion of more patients with Child-Pugh B.

Conflicts of Interest

The GIDEON study is funded by Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals.

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