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Original Article

Sorafenib for 9,923 Patients with Hepatocellular Carcinoma: An Analysis from National Health Insurance Claim Data in South Korea

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See editorial on page 3.

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Background/Aims: Sorafenib is the standard of care in the management of advanced hepatocellular carcinoma (HCC). The purpose of this study was to investigate the characteristics, treatment patterns and outcomes of sorafenib among HCC patients in South Korea.

Methods: This population-based retrospective, single-arm, observational study used the Korean National Health Insurance database to identify patients with HCC who received sorafenib between July 1, 2008, and December 31, 2014. A total of 9,923 patients were recruited in this study.

Results: Among 9,923 patients, 6,669 patients (68.2%) received loco-regional therapy prior to sorafenib, and 1,565 patients (15.8%) received combination therapy with concomitant sorafenib; 2,591 patients (26.1%) received rescue therapy after sorafenib, and transarterial chemoembolization was the most common modality applied in 1,498 patients (15.1%). A total of 3,591 patients underwent rescue therapy after sorafenib, and the median overall survival was 14.5 months compared to 4.6 months in 7,332 patients who received supportive care after sorafenib. The mean duration of sorafenib administration in all patients was 105.7 days; 7,023 patients (70.8%) received an initial dose of 600 to 800 mg. The longest survival was shown in patients who received the recommended dose of 800 mg, subsequently reduced to 400 mg (15.0 months). The second longest survival was demonstrated in patients with a starting dose of 800 mg, followed by a dose reduction to 400–600 mg (9.6 months).

Conclusions: Real-life data show that the efficacy of sorafenib seems similar to that observed in clinical trials, suggesting that appropriate subsequent therapy after sorafenib might prolong patient survival. **(Gut Liver 2024;18:116-124)**

Key Words: Carcinoma, hepatocellular; Sorafenib; Survival

INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for approximately 90% of 850,000 yearly new liver cancer cases globally.[1] A significant medical and economic burden have been imposed by this fatal malignancy.[2] Although HCC with early stage can be managed by curative therapies such as resection, liver transplantation, and local ablation including radiofrequency ablation, patients with advanced stage have dismal prognosis.[3,4] Currently, the new standard of care for the first-line systemic therapy for unresectable HCC is the combination of atezolizumab and bevacizumab. However, sorafenib, the first approved systemic therapy for unresectable HCC, is still a viable option in HCC in certain circumstances. Sorafenib is indicated for treatment in patients with recurrent HCC after liver transplantation, those who are contraindicated for atezolizumab and bevacizumab, or those who do not respond to atezolizumab

and bevacizumab treatment.[5-7]

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 supportive care (p<0.001).[8] A phase III trial conducted in the Asia-Pacific region also confirmed the survival benefit of sorafenib in unresectable HCC.[9] Apart from the well-designed clinical trial data, several studies reported real-life efficacy and safety of sorafenib in patients with HCC.[10-13]

Although both clinical trial and real-practice data showed comparable treatment outcomes of sorafenib indicated by OS, TTP, and adverse event, there are still limited information on the sequence of therapy, i.e., subsequent treatment modality after sorafenib failure in a large cohort. Moreover, survival after sorafenib according to different rescue therapies is largely unknown.

With the progress of big data analysis technique, there have been numerous studies using health insurance claim data to reveal efficacy of a certain drug and to analyze clinical practice patterns. In particular, National Health Insurance (NHI) claim data have an advantage that an inspection on the entire population might enable to catch a nationwide real-world practice pattern in a specific disease.

In this study, we tried to collect information from all the Korean patients who received sorafenib for HCC in a defined period using NHI claim data, and to analyze the treatment pattern related with sorafenib in Korea.

MATERIALS AND METHODS

1. Study design and patients

This was a retrospective, single-arm, and observational study. Data sources were from the Korean NHI claim data, which covers approximately 99% of the Korean population. The NHI claim data include diagnosis, treatment modalities, and prescription drugs. Included patients were those who had been diagnosed as HCC, which was identified using the International Classification of Diseases and Related Health Problems, Tenth Revision codes C22, and the patients received sorafenib between July 1, 2008, and December 31, 2014. C221 code intrahepatic bile duct cancer was excluded. A total of 9,923 patients were recruited in this study: 8,358 patients received sorafenib monotherapy and 1,565 patients received sorafenib and additional other treatment modalities. Comorbidities were identified using the International Classification of Diseases, Tenth Revision. Hypertension defined as International Classification of Diseases, Tenth Revision codes I10, I11, I12, I13, I15, diabetes mellitus defined as E10, E11, E12, E13, E14, and chronic kidney disease defined as N18. As this study utilized a de-identified national database, it was deemed exempt from IRB review.

2. Definition of variables

Index date was defined as the date when sorafenib was first administered, and the last follow-up date was June 30, 2015. HCC-prevalent duration was defined as difference between the index date and HCC diagnosis date. If a patient stopped sorafenib for more than 90 days, it was defined as discontinuation of sorafenib. The mean dose of sorafenib was defined as total sorafenib doses divided by duration of treatment. The OS was defined as duration between death or June 30, 2015, and index date.

3. Statistical methods

Descriptive statistics and survival analysis were performed. For the continuous variables, mean±standard deviation, median, minimum and maximum were presented. For the categorical variables, subject number and proportion were presented. All the results for variables were rounded up to the second digit after the decimal point. The OS, median, 95% confidence interval and Kaplan-Meier survival curve were presented. Statistical analysis was performed using SAS 9.4, and a two-sided p-value of <0.05 was considered statistically significant.

RESULTS

1. Baseline patient characteristics

The mean age of the 9,923 patients was 59 years, and 3,471 patients (34.98%) were in their mid-50s (Table 1). The male patients were predominant, with 8,399 males (84.64%) and 1,524 females (15.36%). Most patients (4,186 subjects, 42.18%) received sorafenib within 6 months after HCC diagnosis. Chronic hepatitis B was the underlying liver disease in 6,550 patients (66.01%), which was the most common cause, followed by chronic hepatitis C in 1,467 patients (14.78%). There were 4,235 (42.68%) patients with hypertension, 4,009 (40.40%) with diabetes, and 223 (2.25%) with chronic kidney disease. A proportion of patients with chronic hepatitis B underwent antiviral therapy, of which entecavir was the most common drug, administered in 3,157 patients (31.81%). The second common antiviral agent was tenofovir in 799 patients (8.05%).

2. Treatment detail before, during and after sorafenib

Before sorafenib treatment, 6,669 patients (67.21%) received other kinds of therapies for HCC including transarterial chemoembolization (TACE), resection and radiation therapy (Table 2). The mean number of treatments before sorafenib was 1.29 and the number of patients who received at least 1 precedent treatment before sorafenib was 6,669 (67.21%). The mean and median time from the last treatment to index date was 408.14 days and 212.00 days, respectively. During sorafenib therapy, 1,565 patients (15.77%) received concomitant treatment with other modalities. The most common modality was radiation therapy in 814 patients (8.20%), followed by TACE in 729 patients (7.35%). After sorafenib therapy, 2,591 patients (26.11%) received rescue treatment, of which TACE was the most common modality applied in 1,498 patients (15.10%) followed by radiation therapy in 1,123 patients (11.32%).

Table 1. Baseline Patient Characteristics

Variable	Value (n=9,923)
Age, yr	
Mean±SD	59.0±10.8
Median (range)	58.0 (14.0–93.0)
<40	341 (3.44)
40–49	1,492 (15.04)
50–59	3,471 (34.98)
60–69	2,756 (27.77)
≥70	1,863 (18.77)
Sex	
Male	8,399 (84.64)
Female	1,524 (15.36)
Concomitant disease	
Hypertension	4,235 (42.68)
Diabetes	4,009 (40.40)
Chronic kidney disease	223 (2.25)
HCC-prevalent duration	
Mean±SD, day	663.29±764.49
Median, day	307.0
<6 mo	4,186 (42.18)
6 mo to <1 yr	1,041 (10.49)
1 to <3 yr	2,064 (20.80)
3 to <5 yr	1,516 (15.28)
≥5 yr	1,116 (11.25)
Underlying liver disease	
Chronic hepatitis B	6,550 (66.01)
Chronic hepatitis C	1,467 (14.78)
Alcohol	1,384 (13.95)
NASH	109 (1.10)

Data are presented as number (%) unless otherwise indicated.
HCC, hepatocellular carcinoma; NASH, nonalcoholic steatohepatitis.

3. Duration of sorafenib administration

The mean duration from initial diagnosis of HCC to administration of sorafenib was 663.29 days (22.1 months). The mean duration of sorafenib administration in all the patients was 105.65 days. The duration in sorafenib monotherapy, sorafenib combined with other therapy, and rescue therapy after sorafenib was 99.14, 140.38, and 120.67 days, respectively. In all the patients, 2,197 patients (22.14%) received sorafenib for less than 4 weeks, while 1,065 patients (10.73%) received sorafenib for more than 32 weeks (Table 3). There was a trend that older age group received sorafenib therapy longer and sorafenib treatment duration was the longest in patients aged 60 to 69 years (110.15 days).

4. Sorafenib dose

In 7,159 patients (72.15%), the initial and mean sorafenib dose were the same. In 1,509 patients (15.21%), the mean sorafenib dose was increased from the initial dose during therapy while in 1,255 patients (12.65%), mean dose was lower than the initial dose. There were 7,023 patients (70.77%) whose initial sorafenib dose was between 600 and 800 mg. Among those patients, the number of patients whose dose was maintained, decreased and increased was 5,722 (57.66%), 1,233 (12.43%) and 68 (0.69%), respectively (Table 4). There were 2,759 patients (27.80%)

Table 2. Treatment Detail before, during, and after Sorafenib (n=9,923)

Treatment modality	Before sorafenib	During sorafenib	After sorafenib
Total	6,669 (67.21)	1,565 (15.77)	2,591 (26.11)
Resection	1,835 (18.49)	29 (0.29)	31 (0.31)
TACE	5,871 (59.17)	729 (7.35)	1,498 (15.10)
HAIC	520 (5.24)	50 (0.50)	94 (0.95)
PEI	129 (1.30)	6 (0.06)	26 (0.26)
Radiation	1,801 (18.15)	814 (8.20)	1,123 (11.32)
RFA	1,353 (13.63)	32 (0.32)	83 (0.84)
Cytotoxic chemotherapy	989 (9.97)	55 (0.55)	790 (7.96)
Liver transplantation	286 (2.88)	11 (0.11)	19 (0.19)

Data are presented as number (%).
TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation.

Table 3. Sorafenib Treatment Duration

Variable	Overall	Sorafenib monotherapy	Combined sorafenib and other therapy	Rescue therapy after sorafenib
No. of patients	9,923	8,358	1,565	2,591
Treatment duration				
Mean±SD, day	105.65±132.24	99.14±126.32	140.38±155.71	120.67±133.06
Median (range), day	65 (1–1,767)	63 (1–1,767)	88 (1–1,217)	78 (1–1,158)
≤4 wk	2,197 (22.14)	1,965 (23.51)	232 (14.82)	426 (16.44)
4 to <8 wk	2,090 (21.06)	1,835 (21.96)	255 (16.29)	499 (19.26)
8 to <12 wk	1,811 (18.25)	1,539 (18.41)	272 (17.38)	467 (18.02)
12 to <16 wk	1,142 (11.51)	958 (11.46)	184 (11.76)	313 (12.08)
16 to <20 wk	631 (6.36)	503 (6.02)	128 (8.18)	209 (8.07)
20 to <24 wk	418 (4.21)	331 (3.96)	87 (5.56)	132 (5.09)
24 to <28 wk	334 (3.37)	258 (3.09)	76 (4.86)	120 (4.63)
28 to <32 wk	235 (2.37)	181 (2.17)	54 (3.45)	69 (2.66)
≥32 wk	1,065 (10.73)	788 (9.43)	277 (17.70)	356 (13.74)
Treatment duration in age group, mean±SD, day				
<40 yr	93.02±113.00	85.39±108.39	119.64±127.63	112.50±112.03
40–49	99.04±118.12	92.75±114.51	124.38±128.78	117.19±126.16
50–59	108.00±134.21	101.17±129.75	140.97±149.74	125.15±134.06
60–69	110.15±140.19	103.04±130.11	152.29±183.85	120.32±141.91
≥70 yr	102.21±129.97	96.90±125.37	146.58±156.95	114.95±125.80

Data are presented as number (%) unless otherwise indicated.

Table 4. Patient Distribution Based on the Initial and Mean Sorafenib Dose

	Mean sorafenib dose, No. (%)				
	≤400 mg	400–600 mg	600–800 mg	800 mg	Total
Initial dose					
≤200 mg	311 (3.13)	55 (0.55)	72 (0.73)	2 (0.02)	440 (4.43)
200–400 mg	1,034 (10.42)	412 (4.15)	869 (8.76)	4 (0.04)	2,319 (23.37)
400–600 mg	5 (0.05)	67 (0.68)	27 (0.27)	0	99 (1.00)
600–800 mg	202 (2.04)	1,031 (10.39)	5,722 (57.66)	68 (0.69)	7,023 (70.77)
800 mg	0	5 (0.05)	12 (0.12)	25 (0.25)	42 (0.42)
Total	1,552 (15.64)	1,570 (15.82)	6,702 (67.54)	99 (1.00)	9,923 (100)

Table 5. Survival According to the Initial and Mean Sorafenib Dose

	Mean sorafenib dose				
	≤400 mg	400–600 mg	600–800 mg	800 mg	Total
Initial dose					
≤200 mg	5.30 (4.30–6.50)	7.10 (4.90– 9.00)	5.45 (3.87–8.70)	3.20 (2.97–3.43)	5.45 (4.77–6.53)
200–400 mg	5.68 (5.10–6.20)	6.82 (5.77–8.07)	5.50 (5.07–5.87)	4.25 (1.90–41.63)	5.73 (5.40–6.00)
400–600 mg	4.10 (2.83–6.70)	7.30 (5.37–9.50)	6.50 (3.10–13.30)	NA	6.50 (5.20–8.83)
600–800 mg	15.00 (12.50–18.97)	9.60 (8.73–10.50)	5.97 (5.77–6.17)	4.78 (3.67–7.10)	6.60 (6.37–6.83)
800 mg	NA	9.60 (3.97–20.17)	4.80 (2.50–16.87)	9.37 (2.53–14.97)	6.63 (3.70–11.63)
Total	6.43 (5.90–6.83)	8.60 (8.07–9.23)	5.87 (5.70–6.07)	4.80 (3.67–7.17)	6.30 (6.13–6.50)

Data are presented as median survival rate (95% confidence interval) and data units are months.
NA, not available.

whose initial sorafenib dose was less than 400 mg. Among those, the proportion of patients whose dose was maintained, increased to 400–600 mg and increased to 600–800 mg was 13.55%, 4.70%, and 9.49%, respectively.

5. Survival according to sorafenib dose

In 7,023 patients (70.77%) whose initial sorafenib dose was 600 to 800 mg, the median survival was 6.60 months (Table 5). The survival of 6,702 (67.54%) patients with a mean sorafenib dose of 600 to 800 mg was 5.87 months,

which was lower than the 8.60 months observed in patients with a mean dose between 400 and 600 mg. The survival was the longest in patients with recommended starting dose of 600 to 800 mg and a mean dose ≤400 mg (15.00 months). The second longest survival was demonstrated in patients with starting dose of 800 mg or 600–800 mg and a mean dose of 400–600 mg (9.60 months). Regarding the survival in association with sorafenib dose for the longest time, 600 mg of sorafenib in 197 patients (8.03 months) or 400 mg in 2,073 patients (7.97 months) showed a better survival compared to 800 mg in 6,228 patients (6.20 months). In 6,163 patients, the median sorafenib dose was 800 mg, and the survival of median 400 mg in 2,004 patients (8.17 months) or 600 mg in 280 patients (7.70 months) was better compared to 800 mg (6.17 months) (Table 6).

6. Post-sorafenib survival according to treatment modality

A total of 2,591 patients underwent rescue therapy after sorafenib, and the median OS was 14.53 months, which were longer than the 4.63 months observed in 7,332

Table 6. Survival According to the Sorafenib Dose Administered for the Longest Time and Median Dose

	Overall survival			
	No. of patients	No. of events (%)	Median, mo	95% CI
Total	9,923	8,180 (82.43)	6.30	6.13–6.50
Dose for the longest time, mg				
<200	169	134 (79.29)	7.03	5.33–9.50
200 to <400	590	459 (77.80)	7.27	6.57–8.33
400	2,073	1,667 (80.90)	7.97	7.43–8.47
401 to <600	125	118 (94.40)	2.77	2.20–3.37
600	197	158 (80.20)	8.03	6.40–9.47
601 to <800	493	455 (92.29)	2.67	2.43–2.97
800	6,276	5,179 (82.52)	6.20	6.00–6.43
Median dose, mg				
<200	144	116 (80.56)	6.63	4.70–9.50
200 to <400	579	451 (77.89)	7.10	6.50–7.90
400	2,004	1,614 (80.54)	8.17	7.63–8.73
401 to <600	152	142 (93.42)	3.15	2.73–3.93
600	280	226 (80.71)	7.70	6.40–9.07
601 to <800	554	508 (91.70)	2.97	2.63–3.17
800	6,210	5,123 (82.49)	6.17	6.00–6.40

CI, confidence interval.

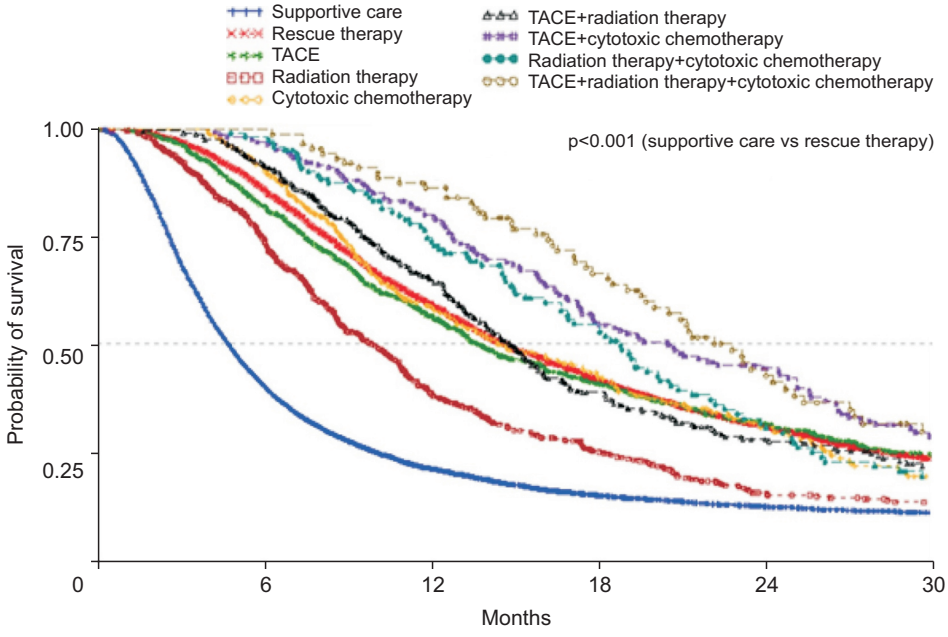

Fig. 1. Survival estimates in subgroups undergoing rescue therapy after sorafenib. TACE, transarterial chemoembolization.

patients who received supportive care after sorafenib. The most commonly applied subsequent treatment after sorafenib was TACE (30.80%), followed by radiation therapy (21.46%), and cytotoxic chemotherapy (12.81%). The median OS in patients who underwent TACE, radiation, and cytotoxic chemotherapy as rescue treatment was 13.70 months, 9.83 months, and 14.37 months, respectively. The longest median OS of 22.83 months was demonstrated in 90 patients who underwent subsequent TACE-radiation-cytotoxic chemotherapy after sorafenib (Fig. 1).

DISCUSSION

Sorafenib has been the only standard of therapy for patients with unresectable HCC demonstrating survival benefit in the first-line setting until a novel drug, lenvatinib, emerged as an alternative first line from positive phase 3 non-inferiority study compared to sorafenib (REFLECT trial).[8,9,14] Novel drugs approved in the second-line setting after sorafenib include regorafenib, nivolumab, cabozantinib, pembrolizumab, and ramucirumab, although survival benefit for ramucirumab was limited to the subgroup with alpha-fetoprotein ≥400 ng/mL.[15-19] Despite the development of an alternative first-line treatment, lenvatinib, a number of patients in the world have been treated with sorafenib.[14] However, there are a few studies which report a real-world data on sorafenib for HCC patients. Global Investigation of Therapeutic Decisions in HCC and of its Treatment with Sorafenib (GIDEON) was a global, prospective, non-interventional study undertaken primarily to evaluate the safety of sorafenib in patients with unresectable HCC in real-life practice.[20] Around the world, more than 3,000 patients were recruited, and data from 1,571 patients were presented in the second interim analysis. Of the patients, 61% had Child-Pugh A and 23% Child-Pugh B status. Furthermore, the majority of patients (74%) received the approved 800 mg initial sorafenib dose, regardless of Child-Pugh status. Obviously, GIDEON study provided useful information on the use of sorafenib in real-world practice. The study has the merit of prospectively collected data from almost all the continents.

The present study is the largest one (n=9,323), which retrospectively enrolled all the consecutive patients who received sorafenib between July 1, 2008, and December 31, 2014, in South Korea. The purpose of study was to reveal the practice patterns regarding sorafenib treatment, subsequent therapies after sorafenib and survival in the whole population. Thus, this is the first and only study to demonstrate the real-practice on sorafenib in HCC patients using big data. Actually, the Korean NHI claim data cover approximately 99% of the Korean population, which might enable to generate real-life based evidences on sorafenib therapy.

Though sorafenib has been the standard of care in HCC patients with advanced stage, a significant portion of patients (n=6,669, 67.21%) was found to receive precedent treatments including TACE and radiation therapy. This disagreement between guidelines and real practice was also suggested in another global study with 18,031 HCC patients, which reported that first HCC treatment was most frequently TACE regardless of stage in North America, Europe, China and Korea.[21]

Determination of post-sorafenib treatment modality is important for patient survival. In an Italian study, post-sorafenib survival was independently predicted by performance status, prothrombin time, extrahepatic tumor spread, macrovascular invasion, and the reason for discontinuation.[22] If a patient has preserved liver function and acceptable performance status, subsequent treatment after sorafenib would improve patient survival. Regorafenib, an oral multi-kinase inhibitor blocking the activity of protein kinases involved in angiogenesis and metastasis, was approved as the first 2nd-line systemic therapy for patients who progressed after sorafenib treatment based on the phase III clinical trial.[15] The period of this study (July 2008 to December 2014) was before the approval of regorafenib in Korea, thus various modalities other than regorafenib were used after sorafenib. The median OS in patients (n=2,591) who received post-sorafenib treatment was 14.53 months, which was longer than 4.63 months in patients (n=7,332) who received supportive care. Interestingly, the longest OS (22.83 months) was shown in 90 patients who underwent TACE, followed by radiation therapy and subsequent cytotoxic chemotherapy. This finding might be explained as follows. Localized tumors with or without distant metastasis could be controlled by loco-regional therapies such as TACE and radiation therapy after sorafenib failure despite vascular invasion, if a patient has sufficient liver function and good performance status. Tumor burden, aggressiveness, and liver function usually determine the prognosis of patients who progress after sorafenib treatment. In a study of 89 HCC patients, 70 showed disease progression after sorafenib and factors such as Child-Pugh scores ≥7, macrovascular invasion, and alpha-fetoprotein >400 ng/mL were independent predictors of poor post-progression survival after sorafenib. In the era of regorafenib as a rescue therapy after sorafenib failure, factors predictive of response to regorafenib or survival need to be identified. Recent studies reported that longer TTP during sorafenib therapy was associated with longer OS and TTP during regorafenib treatment.[23,24]

The overall median duration of sorafenib treatment was 105.65 days (15 weeks) in the entire population, which was similar with data from GIDEON study (17.6 weeks in Child-Pugh A and 9.9 weeks in Child-Pugh B patients).[11] The observation of a longer median sorafenib duration (140.19 days) in patients aged 60 to 70 years compared to other age groups might reflect the tendency of slow tumor growing in older patients.

Our study has several limitations. Atezolizumab plus bevacizumab has emerged as a new first-line treatment for patients with unresectable HCC with preserved liver function. Given that sorafenib is still a viable option for patients with atezolizumab plus bevacizumab failure or recurrence after transplant, the sequential therapy after sorafenib could be applied to this population. Another aspect was the retrospective nature of the study, which should be taken into account in the interpretation of our results given the differences in clinical management across centers. Furthermore, there was a population of patients whose sorafenib was not covered by NHI, and this group of patients were not included in this study.

An important finding in this large-scale study was the distribution of initial and mean sorafenib dose during treatment. More than half of the patients (n=5,722, 57.66%) had the same initial and mean sorafenib dose of 600 to 800 mg, while full initial and mean dose of 800 mg were prescribed in only 25 (0.25%). There has been a controversy between the starting dose of sorafenib and survival. In a retrospective study of 4,903 HCC patients, 3,094 (63%) received standard starting dose of sorafenib and 1,809 had a reduced starting dose of sorafenib. Overall, reduced-dose group had lower OS compared to standard-dose group (median, 200 days vs 233 days, hazard ratio=1.10). However, there were more unfavorable factors such as advanced stage and poor liver function in reduced-dose group. After propensity matching, there was no difference in terms of OS between standard dose and reduced dose.[25] In a GIDEON sub-analysis, 1,113 European HCC patients were studied. A majority of patients (82%) started on standard dose (800 mg) of sorafenib, and the median OS was longer in standard-dose group than in reduced-dose group (12.1 months vs 9.4 months).[17-26] This result should be interpreted with caution given that patients who received reduced starting dose had more advanced disease and poorer liver function. Keeping initial dose on standard 800 mg in HCC patients was consistently shown in GIDEON study, in which the majority of Child-Pugh A (72%) and Child-Pugh B (70%) patients received an initial sorafenib dose of 800 mg.[11] In our study, the longest survival (15.0 months) was shown in patients with starting dose of 600 to 800 mg and a mean dose ≤400 mg. The result of best survival in reduced starting dose and low maintenance dose would not be different with those from previous studies. The favorable survival shown in patients receiving low maintenance dose would have been related to adverse events during treatment, which were proven to be associated with better outcomes.[18,19,27,28] Also, the result highlights that increasing sorafenib exposure with reduced dose in case of adverse events might prolong the patient survival. Since the body weight of Korean patients is usually lower than that of patients in Western countries, continuation of reduced dose may be a good approach to expect favorable outcomes.[20-29] In line with this point, the longest survival was in patients whose dose administered for the longest time was 600 mg (8.03 months), and in patients whose median sorafenib dose was 400 mg (8.17 months).

In conclusion, this real-life data presented prolonged survival of advanced HCC patients who had undergone sequential rescue therapy after sorafenib, highlighting the impact of cancer-directed therapy despite failure of systemic therapy.

CONFLICTS OF INTEREST

J.W.P. reports sponsored lectures for Roche, Ipsen, Bayer, Eisai; consultant/advisory roles for AstraZeneca, Roche, Genetech, Bigene, Bayer, Eutilex, Genexine, Onconic; and research grants from AstraZeneca, Roche, BMS, ONO, Exelixis, MSD-Merck. Except for that, no potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: S.H., D.Y.K., J.W.P. Acquisition of data, analysis and interpretation: S.H., D.Y.K., H.Y.L., J.H.Y., B.Y.R., Y.K., K.K., B.Y.K., S.Y.Y., D.S.K., D.Y.C., J.Y., S.K. Statistical analysis, technical, or material support: Y.K., K.K., B.Y.K., S.Y.Y., D.S.K., D.Y.C., J.Y., S.K. Drafting of the manuscript: S.H., D.Y.K. Critical revision of the manuscript for important intellectual content: S.H., D.Y.K., J.W.P. Study supervision: J.W.P. Approval of final manuscript: all authors.

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