Primary Treatment with Molecular-Targeted Agents for Hepatocellular Carcinoma: A Propensity Score-matching Analysis

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Sorafenib and lenvatinib, as molecular-targeted agents, constitute effective primary treatment options for advanced hepatocellular carcinoma (HCC). However, the choice of optimal primary treatment agent remains controversial. Here, we aimed to assess the respective outcomes between these agents as primary treatment in patients with advanced HCC through use of propensity score–matching analysis (PSMA). We enrolled 670 consecutive patients who were diagnosed with advanced HCC and received sorafenib (n = 524) or lenvatinib (n = 146) as the primary treatment among 18 participating institutions between May 2009 and October 2019. To reduce confounding, we used PSMA regarding seven variables related to advanced HCC prognosis, resulting in the selection of 292 patients (n = 146 for each agent). Following PSMA, no significant difference was observed in the outcome of overall survival time between patients treated with sorafenib or lenvatinib (median survival time 15.3 or 14.9 months, respectively; *P* = 0.2358). Patients treated with lenvatinib exhibited significantly greater therapeutic effects (response rate: 5% and 31%; disease control rate: 46% and 69% for sorafenib and lenvatinib, respectively; *P* < 0.0001), but showed significantly lower probability of transition to secondary treatment (sorafenib, 60%; lenvatinib, 45%; *P* < 0.0269) and higher any adverse events rate (sorafenib, 86%; lenvatinib, 95%; *P* = 0.0207). *Conclusion*: As a primary molecular-targeted agent–based treatment for advanced HCC, our findings suggested that sorafenib is generally appropriate as it offers significantly lower frequency of adverse events and higher probability of transition to secondary treatment, in consideration of the enhanced post-progression survival mediated by sequential treatment. Alternatively, lenvatinib affords a significantly higher therapeutic effect and should be used when immediate tumor reduction is required. (*Hepatology Communications* 2020;4:1218-1228).

Significant progress has been made regarding treatments for hepatocellular carcinoma (HCC), particularly in hepatic resection, percutaneous radiofrequency ablation, transcatheter arterial chemo-embolization, hepatic arterial infusion chemotherapy, radiation therapy, and liver transplantation.[1,2] In addition, the treatment landscape for advanced HCC has also changed dramatically with the approval of molecular-targeted agents (MTAs) such as sorafenib and lenvatinib.[3-5]

Sorafenib has been demonstrated to induce tumor cell apoptosis and targets multiple kinases, such as vascular endothelial growth factor (VEGF) receptors, platelet-derived growth factor (PDGF) receptors, fibroblast growth factor (FGF) receptors, BRAF, KIT, and other molecules.[6,7] As an MTA-based primary treatment for advanced HCC, sorafenib has been shown to provide survival benefit in patients with advanced HCC in the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP)[3] and Asia-Pacific studies,[4] being subsequently approved to treat patients with advanced HCC in Japan in May 2009. Despite multiple clinical trials conducted to evaluate other MTAs, no drugs have been found to exhibit an efficacy superior to that of sorafenib against advanced HCC in primary treatment.[8-15]

Lenvatinib is an oral inhibitor of VEGF receptors, PDGF receptors, FGF receptors, c-Raf, RET, KIT, and other molecules.[16,17] In the REFLECT study (a multicenter randomized, open-label, phase 3 trial to compare the efficacy and safety of lenvatinib [E7080] versus sorafenib in first-line treatment of subjects with unresectable hepatocellular carcinoma) study, lenvatinib has been shown to be non-inferior to sorafenib in terms of overall survival time in patients with advanced HCC as primary treatment.[5] Administration of lenvatinib to patients with advanced HCC demonstrated antitumor activity and a tolerable safety profile in phase 2 and 3 studies,[5,18] and was subsequently approved to treat patients with advanced HCC in Japan in March 2018.

As a result, the optimal choice of MTAs as primary treatment for advanced HCC remains controversial. Therefore, in this study we aimed to assess the real-world treatment outcomes between sorafenib and lenvatinib in patients with advanced HCC. In addition, to reduce confounding, we applied propensity score–matching analysis (PSMA).

Experimental Procedures

PATIENTS

Eligibility criteria for this study were similar to those of the SHARP[3] and REFLECT studies.[5] Since sorafenib's approval in Japan, we have treated 784 patients with advanced HCC using MTAs (sorafenib, n = 550; regorafenib, n = 34; lenvatinib, n = 191; ramucirumab, n = 9) among 18 participating institutions of the Kurume Liver Cancer Study Group of Japan between May 2009 and October 2019. Until lenvatinib's approval in Japan, 490 patients with advanced HCC were treated with sorafenib as the primary treatment option between May 2009 and February 2018. Following lenvatinib's approval in Japan, 180 patients with advanced HCC were treated with MTAs (sorafenib, n = 34; lenvatinib, n = 146) as the primary treatment option between March 2018 and October 2019. Specifically, we prospectively enrolled 670 consecutive patients who were diagnosed with advanced HCC and received sorafenib (n = 524) or lenvatinib (n = 146) as the primary treatment option. HCC was either confirmed histologically or diagnosed using noninvasive criteria according to the European Association for the Study of Liver.[19] The primary outcome of this study was overall survival time, which was defined as the time from initiation of sorafenib or lenvatinib treatment to the date of death or the patient's last follow-up. The study protocol was approved by the Ethics Committee of Kurume University (No. 10009, 18146) and the University Hospital Medical Information Network Center (No. UMIN000007427), and conformed to the guidelines of the 1975 Declaration of Helsinki. Patients were given comprehensive information regarding the details of the clinical study, and each provided written informed consent before participation.

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DIAGNOSIS

Intrahepatic lesions and vascular invasion were diagnosed using a combination of contrast-enhanced computed tomography, magnetic resonance imaging, ultrasonography, and digital subtraction angiography. Additionally, alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP) serum levels were measured up to 1 month before treatment. Intra-abdominal metastases were detected through abdominal computed tomography, magnetic resonance imaging, and ultrasonography, which were performed to evaluate intrahepatic lesions. Pulmonary lesions were detected on chest radiography or computed tomography, which was routinely performed up to 1 month before treatment. Additional examinations, such as bone scintigraphy and brain computed tomography or magnetic resonance imaging, were indicated when symptoms attributable to extrahepatic metastasis appeared. These examinations were also conducted when AFP or DCP levels were elevated in a manner that could not be explained by the status of the intrahepatic lesions.[19] Hepatic reserves were evaluated using both Child-Pugh class (score) and albumin-bilirubin (ALBI) grade.[20] Tumor stage was determined according to the Barcelona Clinic Liver Cancer (BCLC) staging classification.[21,22]

TREATMENT WITH MTAs

Performance status was used to determine the initial MTA dose, at the discretion of the chief physician. Discontinuation and dose reduction was allowed based on tolerance. Adverse events of MTAs were documented according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.[23-25] Treatments were discontinued following development of adverse events of CTCAE grade 3 or above.

ASSESSMENT OF TUMOR RESPONSE

Imaging studies were performed 1 month following the initiation of MTA and every 4-6 weeks thereafter to assess tumor response. The assessment was conducted according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST).[26] Patients who died before their first radiographic assessment were classified as having progressive disease (PD). The time to radiologic progression was defined as the time from MTA initiation to disease progression. Data from patients who died without tumor progression were censored.

PSMA

To reduce confounding, we used PSMA to match patients treated with sorafenib (n = 524) to those treated with lenvatinib (n = 146).[27,28] The following seven variables related to the prognosis of advanced HCC were taken into account at the start of follow-up: age, sex, etiology, Child-Pugh class, BCLC stage, AFP level, and DCP level. The propensity score of the patients treated with sorafenib and lenvatinib was 0.2100 ± 0.0996 and 0.2707 ± 0.1005, respectively (mean ± SD). We used these propensity scores to conduct one-to-one nearest-neighbor matching within a caliper of 0.20, as this percentage of the SD of the logit of the propensity score has been shown to be generally suitable as a caliper of PSMA in previous studies.[29] PSMA resulted in the selection of 292 patients (sorafenib, n = 146; lenvatinib, n = 146). Following PSMA, the propensity score of the patients treated with sorafenib and lenvatinib was 0.2704 ± 0.1004 and 0.2707 ± 0.1005, respectively (mean ± SD).

STATISTICAL ANALYSIS

Baseline patient characteristics were analyzed using descriptive statistical methods, whereas age, intrahepatic tumor size, AFP, and DCP were calculated using the Student t test, and sex, etiology, Child-Pugh class, Child-Pugh score, ALBI grade, BCLC stage, macrovascular invasion, extrahepatic metastasis, and intrahepatic tumor number were calculated using the chi-square test. Survival curves were calculated using Kaplan-Meier analysis with log-rank test. A P value of less than 0.05 was considered statistically significant. JMP software (SAS Institute, Inc., Cary, NC) version 14 was used for all analyses.

Results

PATIENT CHARACTERISTICS OF SORAFENIB AND LENVATINIB COHORTS

Table 1 lists the characteristics of the 670 enrolled patients with advanced HCC receiving MTAs

TABLE 1. PATIENT CHARACTERISTICS OF SORAFENIB AND LENVATINIB COHORTS

Variable	Sorafenib (n = 524)	Lenvatinib (n = 146)	P Value
Age (years)	70.9 ± 9.4	72.8 ± 9.6	0.0391
	71.9 (33.4-94.3)	73.9 (44.7-89.8)	
Sex (male/female)	414 (79%)/110 (21%)	125 (86%)/21 (14%)	0.0750
Etiology (HBV/HCV/HBV + HCV/Both negative)	94 (18%)/300 (57%)/5 (1%)/125 (24%)	25 (17%)/77 (53%)/2 (1%)/42 (29%)	0.6258
Child-Pugh class (A/B)	415 (79%)/109 (21%)	134 (92%)/12 (8%)	0.0021
Child-Pugh score (5/6/7/8/9)	256 (49%)/159 (30%)/72 (14%)/30 (6%)/7 (1%)	81 (56%)/53 (36%)/6 (4%)/5 (3%)/1 (1%)	0.0402
ALBI grade (1/2/3)	140 (27%)/368 (70%)/16 (3%)	44 (30%)/98 (67%)/4 (3%)	0.7070
BCLC stage (B/C)	169 (32%)/355 (68%)	79 (54%)/67 (46%)	< 0.0001
Macrovascular invasion (Yes/No)	131 (25%)/393 (75%)	21 (14%)/125 (86%)	0.0065
Extrahepatic metastasis (Yes/No)	294 (56%)/230 (44%)	56 (38%)/90 (62%)	0.0001
Intrahepatic tumor size (mm)	38.0 ± 35.9	35.9 ± 29.0	0.5121
	28.0 (0.0-210.0)	30.0 (0.0-201.0)	
Intrahepatic tumor number (0/1/2 or more)	80 (15%)/39 (7%)/404 (77%)	15 (10%)/8 (6%)/123 (84%)	0.1852
AFP (ng/mL)	13,322 ± 77,879	3,281 ± 16,152	0.1222
	141 (1-987,600)	79 (2-146,260)	
DCP (mAU/mL)	16,928 ± 86,754	9,798 ± 48,112	0.3415
	611 (2-1,590,000)	209 (12-524,068)	

Note: Results are expressed as the mean ± SD and the median (range) or n.

(sorafenib, n = 524; lenvatinib, n = 146). The median duration of the follow-up period was 10.5 and 7.3 months, respectively. Age (P = 0.0391) was higher in the lenvatinib cohort, whereas Child-Pugh class (P = 0.0021), score (P = 0.0402), and BCLC stage (P < 0.0001) were worse in the sorafenib cohort. Larger numbers of patients exhibited macrovascular invasion (P = 0.0065) and extrahepatic metastasis (P = 0.0001) in the sorafenib cohort. Sex, etiology, ALBI grade, intrahepatic tumor size and number, and AFP and DCP levels were equivalent between the sorafenib and lenvatinib cohorts.

SURVIVAL OUTCOMES BETWEEN THE SORAFENIB AND LENVATINIB COHORTS

Figure 1A shows the results of Kaplan-Meier analysis with log-rank test of radiologic progression-free survival time in patients with advanced HCC receiving sorafenib (n = 524) and lenvatinib (n = 146). Median survival time (MST) was 3.7 (95% confidence interval [CI] = 3.2-4.0) and 5.3 (95% CI = 4.6-5.7) months, respectively (lenvatinib: P = 0.2656, hazard ratio [HR] = 0.881, 95%

CI = 0.705-1.101). The progression-free survival time did not differ significantly between the sorafenib and lenvatinib cohorts.

Figure 1B shows the results of Kaplan-Meier analysis with log-rank test of overall survival time in patients with advanced HCC receiving sorafenib (n = 524) and lenvatinib (n = 146). MST was 11.7 (95% CI = 10.2-13.2) and 14.9 (95% CI = 11.8-) months, respectively (lenvatinib: P = 0.0010, HR = 0.557, 95% CI = 0.392-0.793). The lenvatinib cohort exhibited significantly better outcome with regard to overall survival time than that of the sorafenib cohort.

PATIENT CHARACTERISTICS BETWEEN SORAFENIB AND LENVATINIB COHORTS FOLLOWING PSMA

Table 2 lists the characteristics of the 292 patients with advanced HCC receiving MTAs (sorafenib, n = 146; lenvatinib, n = 146) following PSMA. No significant differences were observed for any variables between the sorafenib and lenvatinib cohorts using PSMA.
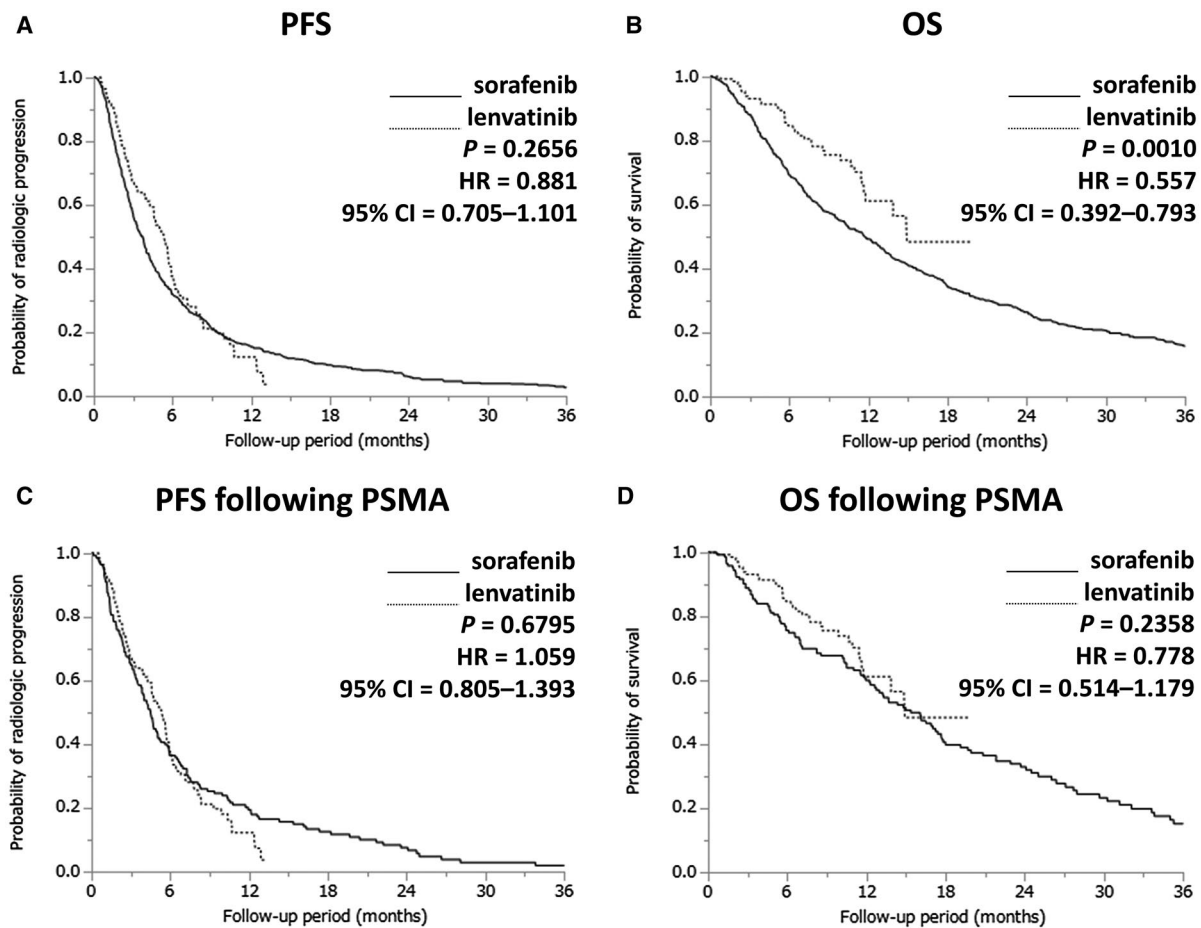
FIG. 1. (A,B) Survival outcomes of sorafenib (solid line; n = 524) and lenvatinib (dotted line; n = 146) cohorts. (A) Progression-free survival. MST: 3.7 months (sorafenib) versus 5.3 months (lenvatinib); $P = 0.2656$; HR = 0.881 (95% CI = 0.705-1.101). (B) Overall survival. MST: 11.7 months (sorafenib) versus 14.9 months (lenvatinib); $P = 0.0010$; HR = 0.557 (95% CI = 0.392-0.793). (C,D) Survival outcomes of sorafenib (solid line; n = 146) and lenvatinib (dotted line; n = 146) cohorts following PSMA. (C) Progression-free survival. MST: 4.5 months (sorafenib) versus 5.3 months (lenvatinib); $P = 0.6795$; HR = 1.059 (95% CI = 0.805-1.393). (D) Overall survival. MST: 15.3 months (sorafenib) versus 14.9 months (lenvatinib); $P = 0.2358$; HR = 0.778 (95% CI = 0.514-1.179).

SURVIVAL OUTCOMES BETWEEN SORAFENIB AND LENVATINIB COHORTS FOLLOWING PSMA

Figure 1C shows the results of Kaplan-Meier analysis with log-rank test of radiologic progression-free survival time in patients with advanced HCC receiving sorafenib (n = 146) and lenvatinib (n = 146) following PSMA. MST was 4.5 (95% CI = 3.8-5.0) and 5.3 (95% CI = 4.6-5.7) months, respectively (lenvatinib: $P = 0.6795$, HR = 1.059, 95% CI = 0.805-1.393). The progression-free survival time did not differ

significantly between the sorafenib and lenvatinib cohorts following PSMA.

Figure 1D shows the results of Kaplan-Meier analysis with log-rank test of overall survival time in patients with advanced HCC receiving sorafenib (n = 146) and lenvatinib (n = 146) following PSMA. MST was 15.3 (95% CI = 12.3-17.7) and 14.9 (95% CI = 11.8-) months, respectively (lenvatinib: $P = 0.2358$, HR = 0.778, 95% CI = 0.514-1.179). The overall survival time did not differ significantly between the sorafenib and lenvatinib cohorts following PSMA.

TABLE 2. PATIENT CHARACTERISTICS OF SORAFENIB AND LENVATINIB COHORTS FOLLOWING PSMA

Variable	Sorafenib (n = 146)	Lenvatinib (n = 146)	P Value
Age (years)	72.8 ± 8.5	72.8 ± 9.6	0.9837
	73.1 (48.3-94.3)	73.9 (44.7-89.8)	
Sex (male/female)	121 (83%)/25 (17%)	125 (86%)/21 (14%)	0.5205
Etiology (HBV/HCV/HBV + HCV/Both negative)	24 (16%)/81 (56%)/2 (1%)/39 (27%)	25 (17%)/77 (53%)/2 (1%)/42 (29%)	0.9721
Child-Pugh class (A/B)	137 (94%)/9 (6%)	134 (92%)/12 (8%)	0.4968
Child-Pugh score (5/6/7/8/9)	84 (58%)/53 (36%)/8 (5%)/0 (0%)/1 (1%)	81 (56%)/53 (36%)/6 (4%)/5 (3%)/1 (1%)	0.2541
ALBI grade (1/2/3)	39 (27%)/105 (72%)/2 (1%)	44 (30%)/98 (67%)/4 (3%)	0.5299
BCLC stage (B/C)	81 (55%)/65 (45%)	79 (54%)/67 (46%)	0.8141
Macrovascular invasion (yes/no)	21 (14%)/125 (86%)	21 (14%)/125 (86%)	1.0000
Extrahepatic metastasis (yes/no)	55 (38%)/91 (62%)	56 (38%)/90 (62%)	0.9040
Intrahepatic tumor size (mm)	37.9 ± 32.0	35.9 ± 29.0	0.5834
	27.5 (0.0-190.0)	30.0 (0.0-201.0)	
Intrahepatic tumor number (0/1/2 or more)	15 (10%)/14 (10%)/117 (80%)	15 (10%)/8 (6%)/123 (84%)	0.4094
AFP level (ng/mL)	5,205 ± 21,675	3,281 ± 16,152	0.3905
	46 (1-186,300)	79 (2-146,260)	
DCP level (mAU/mL)	9,819 ± 34,200	9,798 ± 48,112	0.9966
	381 (11-335,810)	209 (12-524,068)	

Note: Results are expressed as the mean ± SD and the median (range) or n.

THERAPEUTIC EFFECTS BETWEEN SORAFENIB AND LENVATINIB COHORTS FOLLOWING PSMA

Table 3 lists the results at the first radiologic assessment according to the mRECIST following PSMA. In the sorafenib cohort, the response rate was 5% and the disease control rate was 46%, whereas the respective values in the lenvatinib cohort were 31% and 69% ($P < 0.0001$). The lenvatinib cohort thus exhibited significantly higher therapeutic effects than those of the sorafenib cohort following PSMA.

SURVIVAL OUTCOMES WITH REGARD TO THERAPEUTIC EFFECTS FOLLOWING PSMA

Figure 2 shows the results of Kaplan-Meier analysis with log-rank test of overall survival time in patients with advanced HCC between those exhibiting complete response (CR) + partial response (PR) (n = 53), stable disease (SD) (n = 116), and

TABLE 3. THERAPEUTIC EFFECTS OF SORAFENIB AND LENVATINIB TREATMENTS FOLLOWING PSMA

Therapeutic Effect	Sorafenib (n = 146)	Lenvatinib (n = 146)
CR	0 (0%)	8 (5%)
PR	7 (5%)	38 (26%)
SD	60 (41%)	56 (38%)
PD	66 (45%)	33 (23%)
Not evaluable	13 (9%)	11 (8%)

PD (n = 99) following PSMA. MST was 30.2 (95% CI = 13.8-46.6) months with CR + PR, 18.0 (95% CI = 14.4-26.4) months with SD, and 11.8 (95% CI = 9.9-14.9) months with PD (CR + PR vs. SD: $P = 0.0920$, HR = 0.585, 95% CI = 0.311-1.099; CR + PR vs. PD: $P = 0.0001$, HR = 0.319, 95% CI = 0.172-0.591; SD vs. PD: $P = 0.0003$, HR = 0.521, 95% CI = 0.365-0.745). The CR + PR and SD cohorts exhibited significantly better outcome with respect to overall survival time than that of the PD cohort; moreover, the overall survival time did not differ significantly between CR + PR and SD cohorts following PSMA.
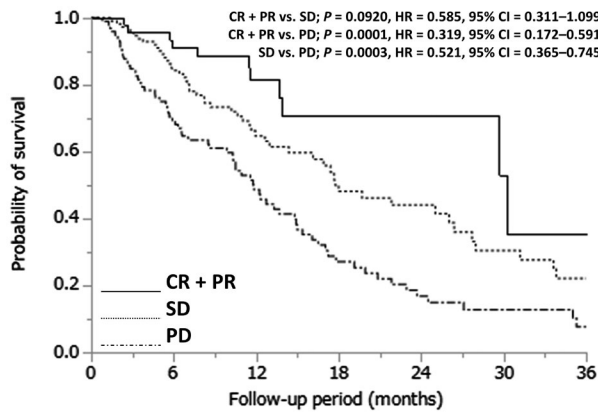
FIG. 2. Survival outcomes of CR + PR (solid line; n = 53), SD (dotted line; n = 116), and PD (dash and dotted line; n = 99) cohorts following PSMA. MST: 30.2 months (CR + PR) versus 18.0 months (SD); P = 0.0920; HR = 0.585 (95% CI = 0.311-1.099). MST: 30.2 months (CR + PR) versus 11.8 months (PD); P = 0.0001; HR = 0.319 (95% CI = 0.172-0.591). MST: 18.0 months (SD) versus 11.8 months (PD); P = 0.0003, HR = 0.521 (95% CI = 0.365-0.745).

TABLE 4. SECONDARY TREATMENT FOLLOWING PSMA

Secondary Treatment	Sorafenib (n = 143)	Lenvatinib (n = 108)
Yes (overlapped)	86 (60%)	49 (45%)
Other MTAs	22 (15%)	6 (6%)
TACE	27 (19%)	22 (20%)
HAIC	22 (15%)	14 (13%)
Radiation therapy	15 (10%)	7 (5%)
No	57 (40%)	59 (55%)

SECONDARY TREATMENT IN SORAFENIB AND LENVATINIB COHORTS FOLLOWING PSMA

By October 2019, the end of the follow-up period, 251 of the 292 patients had discontinued primary treatment with MTAs for advanced HCC following PSMA (sorafenib, n = 143; lenvatinib, n = 108). Table 4 lists the transition rate to secondary treatment following primary treatment with MTAs for advanced HCC following PSMA. In the sorafenib cohort, the transition rate to secondary treatment was 60%, whereas in the lenvatinib cohort the transition rate was 45% (P = 0.0269). The sorafenib cohort was found to have significantly higher transition rate to
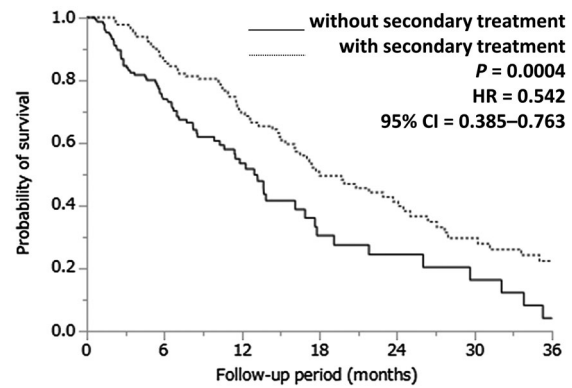

FIG. 3. Survival outcomes of patients with (dotted line; n = 135) and without (solid line; n = 157) secondary treatment following PSMA. MST: 18.0 months (with secondary treatment) versus 12.9 months (without secondary treatment); P = 0.0004; HR = 0.542 (95% CI = 0.385-0.763).

secondary treatment than that of the lenvatinib cohort following PSMA.

SURVIVAL OUTCOMES BETWEEN GROUPS WITH AND WITHOUT SECONDARY TREATMENT FOLLOWING PSMA

Figure 3 shows the results of Kaplan-Meier analysis with log-rank test of overall survival time in patients with advanced HCC between those with (n = 135) and without (n = 157) secondary treatment consequent to primary treatment with MTAs following PSMA. MST was 18.0 (95% CI = 15.4-24.1) and 12.9 (95% CI = 10.3-16.9) months for patients with and without secondary treatment, respectively (with secondary treatment: P = 0.0004, HR = 0.542, 95% CI = 0.385-0.763). Patients with HCC receiving secondary treatment consequent to primary treatment with MTAs exhibited significantly better outcome of overall survival time than that of patients without secondary treatment following PSMA.

DURATION OF TREATMENT FOLLOWING PSMA

Figure 4 shows the results of Kaplan-Meier analysis with log-rank test of the duration of treatment in patients with advanced HCC receiving sorafenib
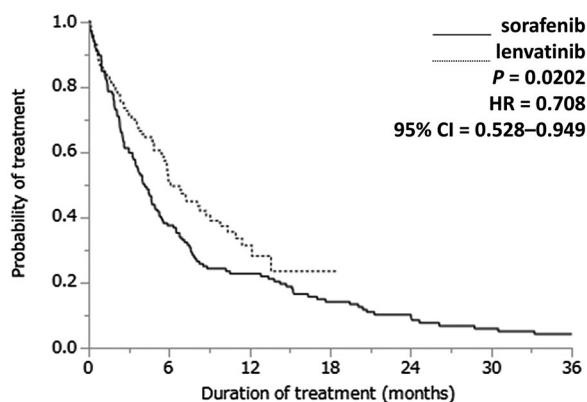
FIG. 4. Duration of treatment of sorafenib (solid line; n = 146) and lenvatinib (dotted line; n = 146) following PSMA. Median duration of treatment: 4.2 months (sorafenib) versus 6.1 months (lenvatinib); P = 0.0202; HR = 0.708 (95% CI = 0.528-0.949).

(n = 146) and lenvatinib (n = 146) following PSMA. Median duration of treatment was 4.2 (95% CI = 3.3-5.1) and 6.1 (95% CI = 5.6-9.1) months, respectively (lenvatinib: P = 0.0202, HR = 0.708, 95% CI = 0.528-0.949). The lenvatinib cohort was found to have a significantly longer treatment period than that of the sorafenib cohort following PSMA.

ADVERSE EVENTS BETWEEN SORAFENIB AND LENVATINIB COHORTS FOLLOWING PSMA

Table 5 lists the adverse events in sorafenib and lenvatinib cohorts following PSMA. Hand-foot skin reaction was the most commonly observed adverse event in all 292 patients, occurring in 107 (37%) patients. Other frequent toxicities included fatigue (n = 86; 29%), diarrhea (n = 58; 20%), anorexia (n = 57; 20%), hypertension (n = 54; 18%), liver dysfunction (n = 44; 15%), hoarseness (n = 33; 11%), proteinuria (n = 18; 6%), and hypothyroidism (n = 14; 5%). In the sorafenib cohort, the most frequent adverse event was hand-foot skin reaction (n = 64; 44%), whereas in the lenvatinib cohort the most frequent adverse event was fatigue (n = 69; 47%). Overall, the adverse events rates in the respective cohorts were 86% and 95% (P = 0.0207). Thus, the lenvatinib cohort was found to exhibit a significantly higher adverse-event rate than that of the sorafenib cohort following PSMA.

TABLE 5. ADVERSE EVENTS OF SORAFENIB AND LENVATINIB TREATMENTS FOLLOWING PSMA

Adverse Event	Sorafenib (n = 146)	Lenvatinib (n = 146)	P Value
Yes (overlapped)	126 (86%)	138 (95%)	0.0207
HFSR	64 (44%)	43 (29%)	0.0108
Fatigue	17 (12%)	69 (47%)	< 0.0001
Diarrhea	23 (16%)	35 (24%)	0.0784
Anorexia	3 (2%)	54 (37%)	< 0.0001
Hypertension	10 (7%)	44 (30%)	< 0.0001
Liver dysfunction	22 (15%)	20 (14%)	0.7387
Hoarseness	3 (2%)	30 (21%)	< 0.0001
Proteinuria	5 (3%)	13 (9%)	0.0516
Hypothyroidism	0 (0%)	14 (10%)	< 0.0001
No	20 (14%)	8 (5%)	0.0171

Discussion

Currently, five drugs have shown clinical activity against advanced HCC in phase 3 clinical trials.[30] Specifically, four drugs exhibited positive results from phase 3 trials using a superiority design (sorafenib in the primary treatment; regorafenib, ramucirumab, and cabozantinib in the secondary treatment), and one showed positive results with a noninferiority design (lenvatinib in the primary treatment).[3-5,30-33]

In the present study, we aimed to assess the real-world treatment outcomes between sorafenib and lenvatinib as primary treatment in patients with advanced HCC using PSMA, to inform which of these MTAs should be used as primary treatment for advanced HCC. In our current study, the lenvatinib cohort exhibited a significantly better outcome with regard to overall survival time than the sorafenib cohort (Fig. 1B). However, following application of PSMA, no significant difference was observed in the outcome of overall survival time between the two cohorts (Fig. 1D). This was considered to result from the findings that sorafenib treatment tended to be disadvantageous with regard to both hepatic reserve factor and tumor factor compared with lenvatinib treatment (Table 1). Notably, this result was retained following PSMA, indicating that the results of the REFLECT study were reproducible.[5]

In the REFLECT study, lenvatinib was shown to be noninferior to sorafenib as a primary treatment in terms of overall survival time in patients with advanced HCC.[5] Similarly, in our current study,

lenvatinib as the primary treatment was not confirmed to be superior to sorafenib in terms of overall survival time in patients with advanced HCC, despite the high response rate (Table 3) and the long duration of treatment (Fig. 4) in the former. In particular, the CR + PR and SD cohorts exhibited significantly better outcome with regard to overall survival time than that of the PD cohort, whereas the overall survival time did not differ significantly between the CR + PR and SD cohorts (Fig. 2). Thus, no significant difference was observed as determined by best response to primary treatment with regard to the overall survival time from the initiation of MTAs. This result suggests that the clinical response might not reflect the overall survival time. A similar phenomenon has also been demonstrated in patients with metastatic renal cell carcinoma who received MTAs.[34]

Furthermore, the PD cohort exhibited the worst prognosis compared with that of CR + PR and SD cohorts (Fig. 2). Thus, primary lenvatinib and sorafenib treatments were considered to be sufficient to maintain SD, which confirms the general recognition of MTAs as being able to maintain SD.[35-37] It is considered that the lack of correlation between primary treatment and the overall survival time may be due to the survival time associated with secondary treatment (i.e., postprogression survival time). Consistent with this, it has been reported that response rates and survival rates are not linked.[38] This suggests that the transition to secondary treatment and extension of postprogression survival time are important for prolonging overall survival time with MTAs for advanced HCC.

In our current study, patients with HCC receiving secondary treatment consequent to primary treatment with MTAs exhibited significantly better outcome with regard to overall survival time than those without secondary treatment following primary treatment with MTAs (Fig. 3). In comparison, the lenvatinib cohort demonstrated a lower transition rate to secondary treatment (Table 4) and higher adverse-event rate (Table 5). Therefore, in the lenvatinib cohort, it was likely that in many cases treatment was discontinued following receipt of only primary treatment. Subsequently, HCC progressed more readily, leading to the potential lack of difference in progression-free survival time between the two groups. It has been reported that the postprogression survival time obtained by sequential treatment is more important

than temporary antitumor effects for prolonging survival time.[39] Thus, survival time is prolonged by consecutively increasing the treatment course, which suggests that sequential treatment exerts considerable influence on the prognosis of patients with advanced HCC receiving MTAs. For example, in the treatment of patients with unresectable colorectal cancer, the median overall survival time obtained from primary treatment has been steadily increasing.[40] In the present study, it is considered that the lower transition rate to secondary treatment in the lenvatinib cohort is probably due to the high incidence of associated adverse events (Table 5). Thus, if the MTA could be administered with better liver function and without adverse events, it would be expected that the transition rate to sequential treatment would increase along with overall survival time.

It is important to consider primary treatment in terms of both sequential treatment considering postprogression survival and antitumor effect. Lenvatinib, as compared with placebo, was associated with significant improvements in progression-free survival along with the response rate among patients with iodine-131-refractory thyroid cancer.[41,42] Nevertheless, differences were identified that must be taken into consideration before choosing between sorafenib and lenvatinib for the treatment of thyroid cancer.[43] In the SELECT study, lenvatinib afforded rapid shrinkage of neoplastic lesions, whereas sorafenib exhibited slower but still relevant activity.[41,43] These findings indicated that lenvatinib would be appropriate to rapidly reduce the volume of a metastatic lesion in a short period of time, such as a vertebral lesion compromising the stability of the column and/or compressing the spinal cord. Applying this result to HCC, lenvatinib would be indicated following the need to rapidly reduce the volume of neoplastic lesions in a short period of time, such as with intrahepatic tumor at high risk of rupture or with macrovascular invasion.[44] However, as the number of cases in the present study was small, further study is required to confirm this application.

Our current study has several limitations. First, the primary treatment, sorafenib or lenvatinib, was selected at the discretion of the chief physician and was not randomized. This resulted in a selection bias for patients treated with each agent. Therefore, to reduce confounding, we used PSMA to match patients treated

with sorafenib to those treated with lenvatinib. Second, the follow-up period in the lenvatinib cohort was relatively short compared with that of the sorafenib cohort, owing to approval not being obtained in Japan until March 2018 to treat patients with advanced HCC. Third, the size of the study cohort was relatively small. To confirm which MTA, sorafenib or lenvatinib, should be used as primary treatment for advanced HCC, prospective randomized studies with a larger number of subjects are required.

In conclusion, as a primary MTA-based treatment for advanced HCC, our findings suggested that sorafenib is generally appropriate because it exhibits a significantly lower frequency of adverse events than lenvatinib in consideration of the enhanced postprogression survival associated with sequential treatment.

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