ANTICANCER RESEARCH *41*: 2187-2192 (2021)
doi:10.21873/anticanres.14993

Efficacy of Ramucirumab *Versus* Sorafenib as Subsequent Treatment for Hepatocellular Carcinoma

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Abstract. *Background/Aim: The present study aimed to examine the therapeutic efficacy of ramucirumab compared with that of sorafenib as subsequent systemic therapy for patients with hepatocellular carcinoma (HCC) and serum α-fetoprotein (AFP) levels ≥400 ng/ml. Patients and Methods: In our prospectively registered, real-world cohort, 13 and 11 patients treated with ramucirumab or sorafenib, respectively, were analyzed. Progression-free survival (PFS) was primarily compared between the ramucirumab and sorafenib groups. Results: The PFS was significantly longer in the ramucirumab group than in the sorafenib group (median, 2.7 vs. 0.9 months, respectively; p=0.005). There were no significant differences in the objective response rates or the disease control rates between the ramucirumab and sorafenib groups (9.1% and 54.5% vs. 0.0% and 22.2%, respectively). Conclusion: Subsequent systemic therapy with ramucirumab showed a better ability to control tumor progression than sorafenib in HCC patients with serum AFP levels ≥400 ng/ml.*

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Key Words: Ramucirumab, sorafenib, hepatocellular carcinoma, α-Fetoprotein, subsequent systemic therapy.

Ramucirumab, which is a human monoclonal antibody that prevents the ligand-mediated activation of vascular endothelial growth factor receptor-2 (VEGFR-2), improved survival when used as second-line systemic therapy after sorafenib in patients with advanced hepatocellular carcinoma (HCC) and baseline serum α-fetoprotein (AFP) levels ≥ 400 ng/ml in the REACH-2 trial (1-3). The therapeutic efficacy of ramucirumab was compared with that of placebo, but it is unclear if there are benefits to ramucirumab over other existing systemic therapies, such as sorafenib, which has often been used for subsequent systemic therapy after lenvatinib has been administered as first-line systemic therapy (4-6). In the era of multiple systemic therapy options, comparison with other drugs is necessary to decide on the use of optimal drugs. The aim of the present study was to examine the therapeutic efficacy of ramucirumab compared with that of sorafenib as subsequent systemic therapy in HCC patients with serum AFP levels ≥400 ng/ml.

Patients and Methods

Study population. This multicenter study analyzed a cohort prospectively registered from July 2018 to July 2020 at the Osaka University Hospital and 7 other institutions participating in the Osaka Liver Forum. Patients who were treated with ramucirumab or sorafenib as subsequent treatment for HCC with serum AFP levels ≥400 ng/ml were enrolled in this study. HCC was diagnosed based on histopathological findings by liver biopsy or radiological findings by the evaluation of dynamic contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) according to the diagnostic criteria of the American Association for the Study of Liver

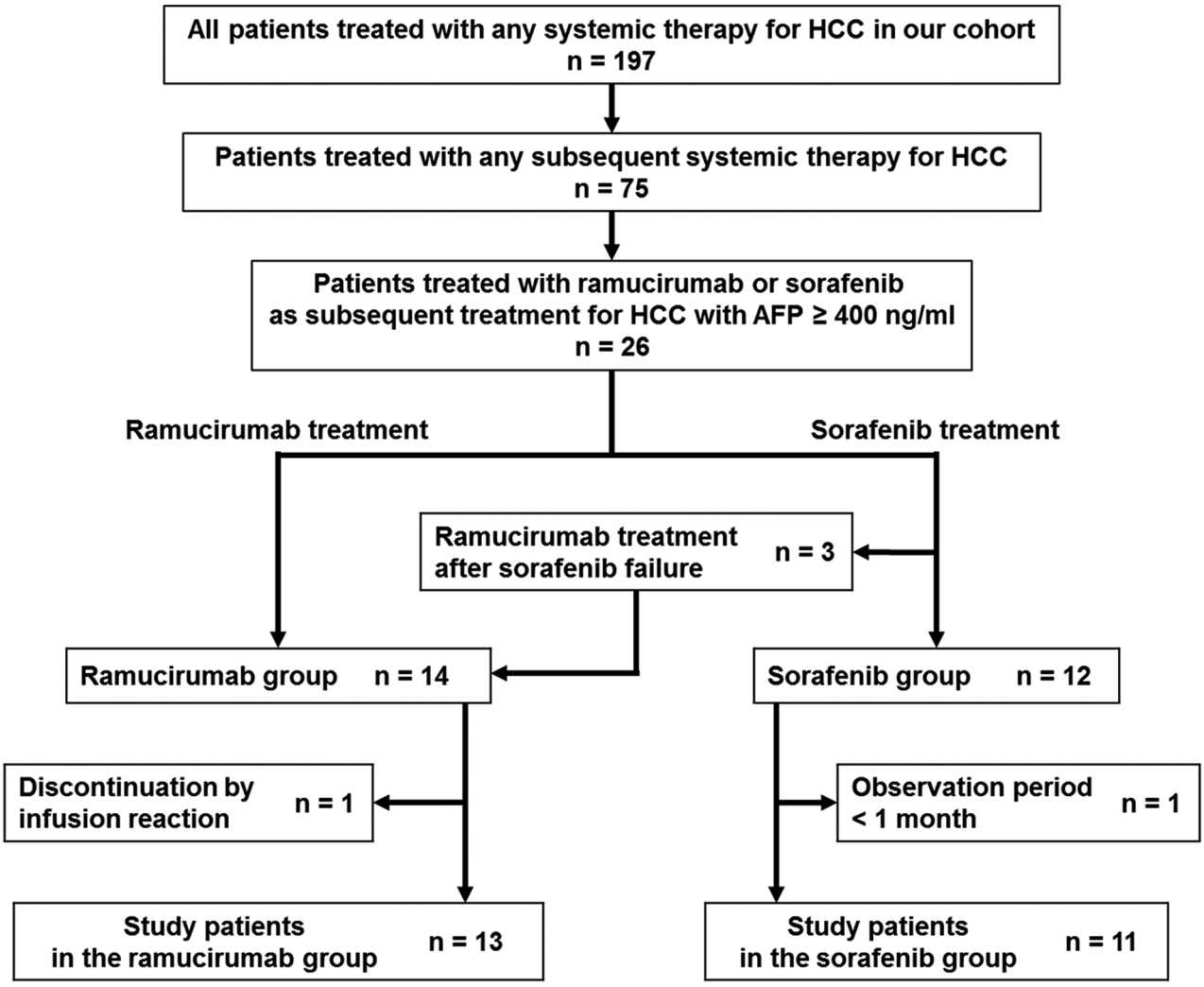

Figure 1. *Flowchart of the study enrollment. HCC: Hepatocellular carcinoma; AFP: α-fetoprotein.*

Diseases or the European Association for the Study of the Liver guidelines (7, 8). The inclusion criteria for this study were as follows: 1) patients with unresectable HCC or not amenable to locoregional therapy; 2) patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; and 3) patients who received ramucirumab or sorafenib at any point after first-line systemic therapy failure. These patients were classified into the ramucirumab group or the sorafenib group. Patients treated with ramucirumab after sorafenib for HCC with serum AFP levels ≥400 ng/ml were enrolled as the ramucirumab group because the aim of this study was to assess the benefit to ramucirumab as any-line systemic therapy compared with sorafenib without ramucirumab treatment. Patients who were followed up for less than 1 month were excluded from the analysis. The primary end-point for this analysis was progression-free survival (PFS) which was calculated from the date of ramucirumab or sorafenib initiation to the date of progressive disease or death.

This study was approved by the Ethics Committee of Osaka University Hospital and the Institutional Review Boards of each institution participating in this study. This study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki, and all patients provided written informed consent prior to enrollment (UMIN000034611).

Ramucirumab and sorafenib treatment. In the ramucirumab group, patients received intravenous ramucirumab at a dosage of 8 mg/kg once every 2 weeks. In the sorafenib group, patients received sorafenib orally at a dosage of 800 mg/day. In each group, some patients were initially treated with reduced doses at the attending physician's discretion. If severe adverse events (AEs) related to either drug occurred, dose reduction or treatment interruption was performed until the symptoms resolved to less than grade 2. The therapeutic response to ramucirumab or sorafenib was assessed in accordance with the modified Response Evaluation Criteria in Solid Tumors (mRECIST) (9), at each institution using enhanced CT or MRI studies, which were performed at 4 and 8 weeks after the initiation of treatment and every 8 weeks thereafter.

Table I. *Comparison of characteristics patients between the ramucirumab group and the sorafenib group.*

Characteristic		Ramucirumab n=13	Sorafenib n=11	*p*-Value
Age, years	Median (range)	74 (62-90)	70 (50-89)	0.150
Gender, n (%)	Male	10 (76.9)	9 (81.8)	0.585
	Female	3 (23.1)	2 (18.2)	
ECOG PS, n (%)	0	11 (84.6)	9 (81.8)	0.637
	1	2 (15.4)	2 (18.2)	
BMI, kg/m^2	Median (range)	22.8 (17.1-32.5)	23.1 (17.1-32.5)	0.820
Etiology, n (%)	HCV	6 (46.2)	2 (18.2)	0.156
	Other	7 (53.8)	9 (81.8)	
Line of systemic therapy, n (%)	2nd	4 (30.8)	11 (100.0)	0.001
	3rd or 4th	9 (69.2)	0 (0.0)	
Previous systemic therapy, n (%)	Len	4 (30.8)	11 (100.0)	
	Len-Sof	3 (23.1)		
	Sof-Len	2 (15.4)		
	Sof-Reg	2 (15.4)		
	Len-Sof-Reg	1 (7.7)		
	Sof-Len-Reg	1 (7.7)		
Maximum intrahepatic tumor size, mm	Median (range)	28 (0-81)	36 (13-86)	0.776
Intrahepatic tumor number, n (%)	≤4	6 (46.2)	3 (27.3)	0.300
	≥5	7 (53.8)	8 (72.7)	
Macrovascular invasion, n (%)	Absent	10 (76.9)	7 (63.6)	0.395
	Present	3 (23.1)	4 (36.4)	
Extrahepatic metastasis, n (%)	Absent	8 (61.5)	8 (72.7)	0.444
	Present	5 (38.5)	3 (27.3)	
BCLC stage, n (%)	B	6 (46.2)	6 (54.5)	0.682
	C	7 (53.8)	5 (45.5)	
Child-Pugh class, n (%)	A	7 (53.8)	7 (63.6)	
	B	6 (46.2)	4 (36.4)	0.473
ALBI score	Median (range)	–1.99 (–2.52- –1.55)	–2.06 (–2.78- –1.03)	0.733
mALBI grade, n (%)	1 or 2a	5 (38.5)	4 (36.4)	0.625
	2b or 3	8 (61.5)	7 (63.6)	
AFP, ng/ml	Median (range)	5789 (550-75420)	2685 (429-44583)	0.424
DCP, mAU/ml	Median (range)	3545 (82-26217)	4789 (41-40172)	0.928
Platelet count, 10^4/μl	Median (range)	10.0 (7.0-21.1)	14.6 (3.7-28.4)	0.167
Bilirubin, mg/dl	Median (range)	1.0 (0.5-1.4)	0.7 (0.5-2.5)	0.392
Albumin, g/dl	Median (range)	3.3 (2.7-3.8)	3.2 (2.3-4.0)	0.303
Prothrombin time, %	Median (range)	89 (59-98)	81 (61-100)	0.422

ECOG PS: Eastern Cooperative Oncology Group performance status; BMI: body mass index; HCV: hepatitis C virus; Len: lenvatinib; Sof: sorafenib; Reg: regorafenib; BCLC: Barcelona Clinic Liver Cancer; ALBI: albumin-bilirubin; mALBI: modified albumin-bilirubin; AFP: α-fetoprotein; DCP: des-γ-carboxy prothrombin.

Statistical analysis. The baseline characteristics are expressed as medians and ranges for continuous variables and as percentages for categorical variables. The Mann-Whitney *U*-test was used to compare continuous variables, and the chi-square test was used to compare qualitative variables. PFS and overall survival (OS) were estimated by the Kaplan-Meier method, and differences in survival curves between the ramucirumab and sorafenib groups were compared by the log-rank test. The statistical significance level was set at a p-value of <0.05. All statistical analyses were performed using SPSS statistical software version 22 for Windows (IBM, Chicago, IL, USA).

Results

Patient characteristics. Between July 2018 and July 2020, 197 patients with HCC receiving any systemic therapy were enrolled in our cohort. Among them, 26 patients had serum AFP levels ≥400 ng/ml and were treated with ramucirumab or sorafenib as subsequent treatment for HCC. Fourteen and 12 patients were classified into the ramucirumab group and sorafenib group, respectively. In the ramucirumab group, 1 patient who discontinued treatment due to an infusion reaction at the first administration was excluded. In the sorafenib group, 1 patient who was followed up for less than 1 month was excluded. Finally, 13 and 11 patients in the ramucirumab group and the sorafenib group, respectively, were analyzed in this study (Figure 1).

The baseline characteristics of the study patients in each group are summarized and compared in Table I. No significant differences were found for almost all characteristics; there was

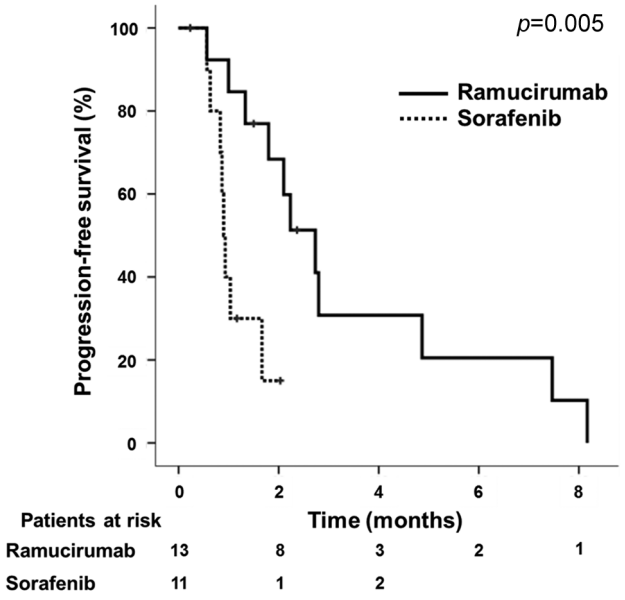

Figure 2. *Comparison of progression-free survival between patients in the ramucirumab group and patients in the sorafenib group.*

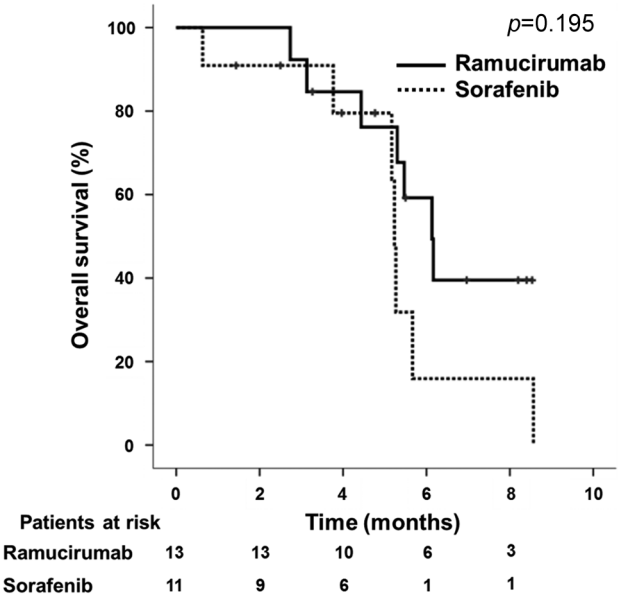

Figure 3. *Comparison of overall survival between patients in the ramucirumab group and patients in the sorafenib group.*

a significant difference only in the lines of systemic therapy between the 2 groups. In the sorafenib group, all patients were treated with the assessed drug as second-line systemic therapy after lenvatinib treatment. However, in the ramucirumab group, 4 patients (30.8%) were treated with the assessed drug as second-line systemic therapy after lenvatinib treatment, and 9 patients (69.2%) were treated as third- or fourth-line systemic therapy. The median observation periods were 5.5 and 4.8 months in the ramucirumab and sorafenib groups, respectively.

Therapeutic efficacy. In the ramucirumab group, 11 patients continued treatment until disease progression, and 2 patients discontinued treatment due to severe AEs before the initial radiologic assessment. In the sorafenib group, 8 patients continued treatment until disease progression, and 3 patients discontinued treatment due to severe AEs; among these 3 patients, 2 patients discontinued treatment before the initial radiologic assessment.

Patients in the ramucirumab group showed significantly longer PFS than patients in the sorafenib group (median, 2.7 *vs.* 0.9 months, respectively; p=0.005) (Figure 2). In the ramucirumab group, the objective response rate (ORR) and the disease control rate (DCR) were 9.1% and 54.5%, respectively. In the sorafenib group, the ORR and DCR were 0.0% and 22.2%, respectively. There were no significant differences in the ORRs or DCRs between the 2 groups.

There was no significant difference in OS between the ramucirumab and sorafenib groups (median, 6.1 *vs.* 5.2 months, respectively; p=0.195) (Figure 3). After treatment with the assessed drugs, 2 (15.4%) and 7 (63.6%) patients received any continuously selectable posttreatment in the ramucirumab and sorafenib groups, respectively. Among the 2 patients in the ramucirumab group, 1 (7.7%) and 1 (7.7%) patient were treated with sorafenib and transarterial chemoembolization (TACE), respectively. Among the 7 patients in the sorafenib group, 3 (27.3%) and 4 (36.4%) patients were treated with regorafenib and TACE, respectively. Nine (69.2%) and 4 (36.4%) patients received no treatment in the ramucirumab and sorafenib groups, respectively. Two patients (15.4%) in the ramucirumab group were still receiving ramucirumab at the end of the study (Table II).

Table II. *Posttreatment in the ramucirumab and sorafenib groups.*

Posttreatment	Ramucirumab n=13	Sorafenib n=11
Any posttreatment, n (%)	2 (15.4)	7 (63.6)
Other systemic therapy, n (%)	1 (7.7)	3 (27.3)
	Sorafenib; 1	Regorafenib; 3
TACE, n (%)	1 (7.7)	4 (36.4)
No treatment, n (%)	9 (69.2)	4 (36.4)
Ongoing, n (%)	2 (15.4)	0 (0.0)

TACE: Transarterial chemoembolization.

Discussion

This is the first report to examine the therapeutic efficacy of ramucirumab compared with that of sorafenib as subsequent systemic therapy for HCC patients with serum AFP levels ≥400 ng/ml in the real world. Our results showed significantly longer PFS with ramucirumab treatment than with sorafenib treatment. In the REACH-2 trial, the median PFS with ramucirumab was 2.8 months, and the ORR and DCR were 4.6% and 59.9%, respectively, in accordance with RECIST 1.1 (1). These results showed the improved therapeutic efficacy of ramucirumab compared with that of placebo, but the benefit to ramucirumab compared with that to other existing systemic therapies was unclear. In a few recent real-world studies, the therapeutic efficacy and safety of ramucirumab were reported (10-13). In these studies, the median PFS was 1.4-3.8 months, and the ORR and DCR were 0.0-10.0% and 28.6-80.0%, respectively, which were similar to the results of the REACH-2 trial. However, the therapeutic efficacy of ramucirumab compared with that of other systemic therapies has not been investigated in real-world studies.

With sorafenib treatment as first-line systemic therapy, the median time to progression was 2.8-5.5 months, and the DCR was 43.0-59.0% in previous trials (4, 14, 15). In a recent report on sorafenib treatment as subsequent systemic therapy in a single arm, the median PFS was 4.1 months, and the ORR and DCR were 0.0% and 69.2%, respectively (16). In the sorafenib group of our study, which included HCC patients with serum AFP levels ≥400 ng/ml, the median PFS was 0.9 months, and the DCR was 22.2%; these values were worse than the previous results with sorafenib treatment. This difference might be due to the high levels of serum AFP, which has been reported to be a poor prognostic factor in HCC patients treated with sorafenib in previous studies (17, 18). Few data regarding sorafenib as a subsequent treatment have been reported, and further studies to investigate its efficacy as a subsequent treatment compared with that of other systemic therapies are required.

In this study, there was no significant difference in OS between the ramucirumab and sorafenib groups, although PFS was significantly longer in the ramucirumab group. It was difficult to simply compare the OS between the ramucirumab and sorafenib groups as subsequent treatment because the ramucirumab group included patients treated as third- or fourth-line systemic therapy, and patients in the ramucirumab and sorafenib groups received different drugs for posttreatment after administration of the assessed drugs. It has been reported that posttreatment with systemic therapy could affect the prognosis of patients after systemic therapy failure (19, 20). When the OS of patients treated with subsequent systemic therapy is assessed, these factors affecting the prognosis need to be considered. This is the reason why we focused on comparing the ability to control tumor progression between the ramucirumab and sorafenib groups. The PFS in the ramucirumab group was significantly longer than that in the sorafenib group although the ramucirumab group comprised patients treated as late line systemic therapy in our cohort.

There are a few limitations to this study. This study had a small sample size, and patients were not randomly assigned to treatment groups. Further studies in larger cohorts are needed to confirm our results.

In conclusion, subsequent systemic therapy with ramucirumab improved PFS compared with that with sorafenib in HCC patients with serum AFP levels ≥400 ng/ml.

Conflicts of Interest

Professor Tetsuo Takehara received research grants from Eisai and MSD K. K. and lecture fees from MSD K. K. Tomohide Tatsumi, Ryotaro Sakamori, Hayato Hikita and Takahiro Kodama received research grants from MSD K.K. All other Authors declare no conflicts of interest.

Authors' Contributions

Conception and design: Kazuki Maesaka, Ryotaro Sakamori. Data collection: Kazuki Maesaka, Kazuyoshi Ohkawa, Masahide Oshita, Shinji Tamura, Hideki Hagiwara, Eiji Mita, Takayuki Yakushijin, Masami Inada. Data analysis and interpretation: Kazuki Maesaka, Ryotaro Sakamori. Drafting of the article: Kazuki Maesaka, Ryotaro Sakamori. Critical revision: Ryoko Yamada, Yuki Tahata, Takahiro Kodama, Hayato Hikita, Tomohide Tatsumi, Tetsuo Takehara. Final approval of the article: All Authors.

Acknowledgements

The Authors wish to express their gratitude to the hospitals that participated in the Osaka Liver Forum: Osaka International Cancer Institute, Osaka Police Hospital, Minoh City Hospital, Kansai Rosai Hospital, National Hospital Organization Osaka Medical Center, Osaka General Medical Center and Toyonaka Municipal Hospital.

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Received March 5, 2021
Revised March 11, 2021
Accepted March 12, 2021