Posttreatment after Lenvatinib in Patients with Advanced Hepatocellular Carcinoma

Keisuke Koroki^a Naoya Kanogawa^a Susumu Maruta^{a,b} Sadahisa Ogasawara^{a,c} Yotaro Iino^d Masamichi Obu^d Tomomi Okubo^e Norio Itokawa^{e,f} Takahiro Maeda^c Masanori Inoue^c Yuki Haga^g Atsuyoshi Seki^h Shinichiro Okabeⁱ Yoshihiro Koma^d Ryosaku Azemoto^d Masanori Atsukawa^{e,f} Ei Itobayashi^b Kenji Ito^g Nobuyuki Sugiura^g Hideaki Mizumoto^h Hidemi Unoza^a Terunao Iwanaga^a Takafumi Sakuma^a Naoto Fujita^a Hiroaki Kanzaki^a Kazufumi Kobayashi^{a,b} Soichiro Kiyono^a Masato Nakamura^a Tomoko Saito^a Takayuki Kondo^a Eiichiro Suzuki^a Yoshihiko Ooka^a Shingo Nakamoto^a Akinobu Tawada^{a,j} Tetsuhiro Chiba^a Makoto Arai^{a,j} Tatsuo Kanda^{a,k} Hitoshi Maruyama^{a,l} Jun Kato^a Naoya Kato^a

^aDepartment of Gastroenterology, Graduate School of Medicine, Chiba University, Chiba, Japan; ^bDepartment of Gastroenterology, Asahi General Hospital, Asahi, Japan; ^cTranslational Research and Development Center, Chiba University Hospital, Chiba, Japan; ^dDepartment of Gastroenterology, Kimitsu Chuo Hospital, Kisarazu, Japan; ^eDivision of Gastroenterology, Department of Internal Medicine, Nippon Medical School Chiba Hokusoh Hospital, Inzai, Japan; ^fDivision of Gastroenterology and Hepatology, Department of Internal Medicine, Nippon Medical School, Tokyo, Japan; ^gDepartment of Gastroenterology, National Hospital Organization Chiba Medical Center, Chiba, Japan; ^hDepartment of Gastroenterology, Funabashi Municipal Medical Center, Funabashi, Japan; ⁱDepartment of Gastroenterology, Matsudo City General Hospital, Matsudo, Japan; ^jDepartment of Medical Oncology, Graduate School of Medicine, Chiba University, Chiba, Japan; ^kDivision of Gastroenterology and Hepatology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan; ^lDepartment of Gastroenterology, Juntendo University School of Medicine, Tokyo, Japan

Keywords

Hepatocellular carcinoma · Lenvatinib · Posttreatment

Abstract

Background: There is no standard posttreatment for patients with advanced hepatocellular carcinoma (HCC) in whom lenvatinib therapy has failed. This study aimed to investigate rates of migration to posttreatment after lenvatinib and to explore candidates for second-line agents in the patients with failed lenvatinib therapy. **Methods:** We retrospectively collected data on patients with advanced HCC who received

lenvatinib as the first-line agent in 7 institutions. **Results:**

Overall survival and progression-free survival (PFS) of 178 patients who received lenvatinib as the first-line agent were 13.3 months (95% confidence interval [CI], 11.5–15.2) and 6.7 months (95% CI, 5.6–7.8), respectively. Sixty-nine of 151 patients (45.7%) who discontinued lenvatinib moved on to posttreatment. The migration rates from lenvatinib to the

K. Koroki, N. Kanogawa, and S. Maruta contributed equally to this work.

Clinical trial number: The Chiba University Research Ethics Committee approved this study (No. 2896).

second-line agent and from the second-line agent to the third-line agent were 41.7 and 44.4%, respectively. Based on multivariate analysis, response to lenvatinib (complete or partial response according to modified RECIST) and discontinuation of lenvatinib due to radiological progression, as well as male were associated with a significantly higher probability of migration to posttreatment after lenvatinib. On the other hand, alpha-fetoprotein levels of 400 ng/mL or higher was correlated with a significantly lower probability of migration to posttreatment after lenvatinib. Of 63 patients who received second-line systemic therapy, 53 (84.2%) were administered sorafenib. PFS, objective response rate (ORR), and disease control rate (DCR) for sorafenib treatment were 1.8 months (95% CI, 0.6–3.0), 1.8%, and 20.8%, respectively. According to the Cox regression hazard model, Child-Pugh class B significantly contributed to shorter PFS. PFS, ORR, and DCR of 22 patients who received regorafenib after lenvatinib in any lines were 3.2 months (range, 1.5–4.9 months), 13.6%, and 36.3%, respectively. Similarly, PFS, ORR, and DCR of 17 patients who received regorafenib after lenvatinib in the third-line (after sorafenib) were 3.8 months (range, 1.1–6.5 months), 17.6%, and 41.2%, respectively. **Conclusion:** Sorafenib may not be a candidate for use as a posttreatment agent after lenvatinib, according to the results of the present study. Regorafenib has the potential to become an appropriate posttreatment agent after lenvatinib.

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Published by S. Karger AG, Basel

Introduction

Hepatocellular carcinoma (HCC) is one of the most malignant neoplasms and is the third leading cause of cancer death worldwide [1, 2]. As of the early 2000s, the development of systemic therapies for advanced HCC was much slower than that for other types of cancer [3]. In 2007, sorafenib, a tyrosine kinase inhibitor (TKI) with an activity against Raf kinase and several receptor tyrosine kinases, including vascular endothelial growth factor receptor 2 (VEGFR2), platelet-derived growth factor receptor (PDGFR), FLT3, Ret, and c-Kit, was associated with significantly longer overall survival (OS) than placebo in 2 global phase III studies [4, 5]. When sorafenib was positioned as the initial standard systemic therapy in advanced HCC, various molecular target agents (MTAs), mostly TKIs, were under development for patients with advanced HCC [6]. However, several novel compounds had failed in phase III trials compared with sorafenib in the first-line setting or compared with placebo in the second-line setting, and there had been no new agent for advanced HCC

for nearly a decade [7–12]. In the late 2010s, after “the era of sorafenib,” which was the only single agent for patients with advanced HCC, phase III studies showed that MTAs such as regorafenib, lenvatinib, cabozantinib, and ramucirumab were effective [13–16]. These results have ushered in “the era of multi-MTAs,” in which several MTAs can be administered sequentially in real-world practice.

Lenvatinib, an oral TKI that targets VEGFRs 1 through 3, fibroblast growth factor receptors 1 through 4, PDGFR β , and the RET and KIT oncogenes, demonstrated a treatment effect on OS by statistical confirmation of noninferiority to sorafenib in patients with advanced HCC in a phase III trial (REFLECT trial) [14, 17]. At present, lenvatinib is positioned as the standard first-line MTA for treatment of HCC and is being approved by regulatory authorities around the world. Several recent studies have confirmed the effectiveness of lenvatinib for advanced HCC in real-world practice, and it is becoming a mainstay in treatment strategies for advanced HCC [18–20].

The major disadvantage of the use of lenvatinib in clinical practice is the lack of a posttreatment after lenvatinib that has shown clear effectiveness since all phase III trials with published results to date have been designed on the premise that sorafenib is a standard first-line agent in patients with advanced HCC [13–16, 21]. In “the era of multi-MTAs,” when several promising agents are available in real-world practice, sequential treatment with MTAs is becoming a mainstream treatment strategy for advanced HCC, as well as for other cancers. Therefore, the establishment of a second-line treatment after the failure of lenvatinib treatment is an urgent clinical issue to be addressed in systemic therapy in patients with advanced HCC. The aim of this study was to explore candidate drugs that might be appropriate as the second-line treatment after lenvatinib with the use of real-world clinical data.

Patients and Methods

Patients and Clinical Parameters

The study included patients with advanced HCC who received lenvatinib as a first-line agent in 7 institutions in Japan between March 23, 2018 (the date of lenvatinib approval in Japan), and September 30, 2019. We retrospectively collected clinical parameters described below during the entire clinical course of all patients after lenvatinib was administered. In this analysis, the data were locked on July 31, 2020. The study was approved by the Research Ethics Committee of the Graduate School of Medicine, Chiba University (No. 2896). We had access to information that could identify individual patients during or after the data collection. Patient data were anonymized and deidentified before analysis.

General treatments with lenvatinib were documented in a previous article [19]. Briefly, the respective standard starting doses of lenvatinib for Child-Pugh A patients weighing 60 kg or more and less than 60 kg were 12 and 8 mg orally once per day. The starting dose of lenvatinib for Child-Pugh class B patients was 8 mg orally once per day. Dynamic contrast-enhanced computed tomography or magnetic resonance imaging was performed at baseline and every 1–2 months after starting treatment for evaluation of tumor response. Lenvatinib was continued until the physician determined clear progression of disease on radiological imaging or until the occurrence of adverse events that prevented continuation of treatment. In the current Japanese filed practice, sorafenib, regorafenib, and ramucirumab are available for use after lenvatinib treatment under the national social insurance system. Regorafenib is recommended for use after sorafenib on the basis of the criteria of the RESORCE trial [13] and is currently the agent most commonly administered after sorafenib in Japan, although administration of regorafenib directly after sorafenib is not strictly regulated by the Japanese regulatory authority (Pharmaceuticals and Medical Devices Agency). Ramucirumab is limited to patients with advanced HCC with confirmed alpha-fetoprotein (AFP) levels of 400 ng/mL or higher [16]. Sorafenib and regorafenib were already available at the time of the approval of lenvatinib in Japan. Ramucirumab was approved on June 18, 2019. In this cohort, each physician decided which treatment to subsequently administer after lenvatinib, including MTAs, resection, local ablation, transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), radiation, or best supportive care. If local tumor control was assumed to contribute to a better prognosis at the time of lenvatinib failure, we selected the best treatment option from among the resection, local ablation, TACE, HAIC, or radiation. We opted to migrate to other MTAs if patients' liver function and Eastern Cooperative Oncology Group Performance Status (ECOG-PS) were both maintained to the extent that MTAs were tolerated. We recommended the best supportive care if patients had poor liver function or low ECOG-PS at the time of lenvatinib failure. If the selection of post-treatment after lenvatinib was in doubt, the treatment was reviewed and decided at the multidisciplinary team meeting of each institution. A standard starting dosage of sorafenib was 800 mg/day (400 mg orally twice daily). Based on the physicians' decisions, a reduced starting dosage of <800 mg/day was given to some patients in the study. A standard starting dosage was 160 mg/day of regorafenib orally once for 3 weeks, followed by 1 week of no treatment for each cycle. A reduced starting dosage of <160 mg/day regorafenib was allowed in addition to the reduced dosage of sorafenib.

We retrieved medical records of all patients and collected data on the following clinical parameters: baseline demographic data of lenvatinib, date of radiological progression, cause and date of discontinuation of lenvatinib, baseline demographic data of the second- and third-line agents, date of radiological progression, cause and date of discontinuation of each drug after lenvatinib, and date of death or the last follow-up. Radiological assessments were evaluated according to modified RECIST (mRECIST) [22]. Separately, the Common Terminology Criteria for Adverse Events version 4.0 protocol was used for the assessment of adverse events.

Statistical Analysis

Kaplan-Meier plots of medians with 95% confidence intervals (CIs) were used for estimating OS. The censoring date was defined as the date of the last follow-up. Progression-free survival (PFS)

Table 1. Baseline characteristics of 178 patients with HCC treated with lenvatinib

Demographics/characteristics	All patients (n = 178) (%)
Sex, male	145 (81.5)
Age, >73 yr old	84 (47.2)
HBV positive	25 (14.0)
HCV positive	70 (39.3)
Alcohol abuse	50 (28.1)
Body weight, <60 kg	73 (41.0)
ECOG-PS, ≤1	169 (94.9)
Child-Pugh score	
5	93 (52.3)
6	57 (32.0)
≥7	28 (15.7)
Number of intrahepatic lesions, >7	90 (50.6)
Maximum size of intrahepatic lesions, >50 mm	67 (37.6)
Intrahepatic tumor occupation, ≥50%	16 (9.0)
MVI	45 (25.3)
EHM	64 (36.0)
BCLC stage C	107 (60.1)
AFP, >400 ng/mL	62 (34.8)
Pretreatment	142 (79.8)

HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group; PS, performance status; MVI, macrovascular invasion; EHM, extrahepatic metastasis; BCLC, Barcelona clinic liver cancer; AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; ECOG-PS, Eastern Cooperative Oncology Group Performance Status.

after lenvatinib and each second- or third-line agent was estimated using Kaplan-Meier plots of medians with 95% CIs, with the date of progression defined according to mRECIST and the censoring date defined as the date of last radiological assessment without progression. Logistic regression analysis was performed to assess the factors for migration to posttreatment after lenvatinib. The Cox proportional hazard regression model was used to estimate hazard ratios for PFS with sorafenib treatment after lenvatinib. Both multivariate logistical and Cox proportional hazard regressions were calculated by using a stepwise model. A *p* value of <0.05 was considered statistically significant. All statistical analyses were conducted using the Statistical Package for the Social Sciences version 25 statistical software (SPSS, IBM, Armonk, NY, USA).

Results

Study Population

During the study period, 178 patients with advanced HCC received lenvatinib as first-line systemic therapy at 7 Japanese institutions. Table 1 shows the baseline characteristics of the study population. The majority of patients (81.5%) were male, and the median age was 73 years (range,

Fig. 1. a PFS with lenvatinib treatment. **b** OS from administration of lenvatinib. **c** Comparison of OS between patients without (dotted line) and with (solid line) posttreatment after lenvatinib. PFS, progression-free survival; OS, overall survival.

33–95 years). At the time of lenvatinib administration, most of the patients were ECOG-PS 0 or 1 (94.9%) and Child-Pugh class A (84.3%). According to the baseline radiological assessments, 25.3 and 36.0% of patients had macrovascular invasion and extrahepatic metastasis, respectively. OS and PFS were 13.3 months (95% CI, 11.5–15.2) and 6.7 months (95% CI, 5.6–7.8), respectively (Fig. 1). The rate of objective response according to mRECIST was 39.3%. During the follow-up period, 151 of 178 patients (84.8%) discontinued lenvatinib, and 87 of them (57.2%) had confirmed radiological progression according to mRECIST. The median treatment duration of lenvatinib was 4.9 months (95% CI, 3.9–5.9). The most common causes of

discontinuation of lenvatinib in patients without radiological progression were anorexia (12 patients, 7.9%), disease progression determined clinically (without radiological progression according to mRECIST) (12 patients, 7.9%), disorder of physical status (10 patients, 6.6%), fatigue (8 patients, 5.3%), and liver dysfunction (7 patients, 4.6%).

Migration to Posttreatment after Discontinuation of Lenvatinib

Up to the date of data cutoff, 69 of 151 patients (45.7%) who discontinued lenvatinib migrated to posttreatment (Fig. 2). The other 82 patients (54.3%) received palliative care after discontinuation of lenvatinib. The majority of

Fig. 2. Overview of transition from lenvatinib to second- and third-line treatments in patients with advanced HCC. BSC, best supportive care; MTA, molecular target agent; HCC, hepatocellular carcinoma.

Table 2. Logistic regression analysis of the predictive factors for migration to posttreatment after lenvatinib in patients with advanced HCC

Variables	Univariate analysis		p value	Multivariate analysis		p value
	odds ratio	95% CI		odds ratio	95% CI	
Sex, male	3.665	1.468–9.150	0.005	4.207	1.523–11.617	0.006
Age, >73 yr old	0.626	0.328–1.194	0.155			
Body weight, <60 kg	0.568	0.295–1.093	0.090			
ECOG-PS >1	0.460	0.086–2.447	0.362			
Child-Pugh class B	0.586	0.232–1.478	0.257			
HBV positive	1.568	0.582–4.222	0.374			
HCV positive	0.821	0.428–1.575	0.554			
Intrahepatic tumor volume, >50%	1.230	0.409–3.697	0.713			
BCLC stage C	0.426	0.218–0.833	0.013			
Baseline AFP, >400 ng/mL	0.333	0.164–0.675	0.002	0.368	0.160–0.756	0.008
Responder to lenvatinib	2.638	1.320–5.70	0.006	3.081	1.387–6.843	0.006
Discontinued lenvatinib after radiological progression	3.172	1.621–6.210	0.001	2.260	1.087–4.699	0.029

HCC, hepatocellular carcinoma; BCLC, Barcelona clinic liver cancer; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; PS, performance status; AFP, alpha-fetoprotein; CI, confidence interval.

patients who migrated to posttreatment after lenvatinib were given MTAs (63 of 69 patients), but 6 patients received other treatments (TACE, 3 patients; HAIC, 2 patients; and resection, 1 patient). None of the patients in the present cohort had been treated by radiation therapy after lenvatinib failure. Similarly, 54 of 63 patients (85.7%) who migrated to the second-line agents discontinued treatment, and 30 of them (55.5%) received posttreatment after

the second-line agents (third-line agents, 24 patients; HAIC, 4 patients; unknown, 2 patients). The rates of migration from lenvatinib to the second-line MTAs and from the second-line MTAs to the third-line MTAs were 41.4 and 44.4%, respectively. Of 144 patients with both Child-Pugh A and ECOG-PS scores ≤ 1 at the time of starting lenvatinib, 123 patients discontinued lenvatinib at the time of data cutoff and 54 patients migrated from lenva-

Table 3. Transition of liver function between the start and end of lenvatinib according to Child-Pugh score

Child-Pugh score	Migration to posttreatment after lenvatinib		
	absent (%)	present (%)	<i>p</i> value
At the time of start of lenvatinib			
5	35 (43.2)	40 (58.8)	0.155
6	31 (38.3)	20 (29.4)	
≥7	15 (18.5)	8 (11.8)	
At the time of end of lenvatinib			
5	12 (14.8)	24 (35.3)	<0.001
6	15 (18.5)	20 (29.4)	
≥7	54 (66.7)	24 (35.3)	
Transition of liver function			
Improvement	4 (4.9)	5 (7.4)	0.003
Remaining	20 (24.7)	34 (50.0)	
Worsening	57 (70.4)	29 (42.6)	

tinib to the second-line MTAs (43.9%). Furthermore, 23 of 47 patients, excluding 7 patients who were ongoing the second-line MTAs, migrated from the second-line MTAs to the third-line MTAs (48.9%). Fig. 1c shows that OS after lenvatinib was significantly longer in patients who migrated to posttreatment than in patients who received palliative care (posttreatment, OS not reached; palliative care, OS 6.0 months; 95% CI, 4.3–7.8; $p < 0.001$).

We used logistical regression analysis to identify the factors that contributed to migration to posttreatment after lenvatinib (Table 2). In this analysis, patients who received not only MTAs but also other treatments (i.e., TACE, HAIC, and resection) were included. Baseline clinical parameters at the time of lenvatinib administration and clinical outcomes during lenvatinib treatment were included in this analysis. We found that male, responder of lenvatinib, and discontinuation of lenvatinib due to radiological progression according to mRECIST were associated with a significantly higher probability of migration to posttreatment after lenvatinib. On the other hand, AFP level >400 ng/mL at the time of lenvatinib administration was a significant negative predictive factor for migration to posttreatment after lenvatinib.

In the present cohort, 149 patients (98.7%) had the liver function assessed at the time of lenvatinib discontinuation. Table 3 shows transition of liver function between the start and the end of lenvatinib according to Child-Pugh scores. Patients who migrated to posttreatment had significantly better Child-Pugh scores at the end of lenvatinib treatment than patients moved to the best supportive care.

Sorafenib after Discontinuation of Lenvatinib

Of 63 patients who received second-line systemic therapy after failure of lenvatinib treatment, 53 patients (84.2%) received sorafenib. The baseline characteristics of patients at the time of sorafenib administration are shown in Table 4. All 53 patients were ECOG-PS 0 or 1, and 36 patients (67.9%) were Child-Pugh class A. At baseline radiological assessment, 30.2% of patients had macrovascular invasion and 39.6% had extrahepatic metastasis. OS and PFS from the date of sorafenib administration were 10.4 months (95% CI, 4.7–16.0) and 1.8 months (95% CI, 0.6–3.0), respectively (Fig. 3a). According to mRECIST, the objective response rate (ORR) and the disease control rate (DCR) were 1.8 and 20.8%, respectively. Table 5 shows the results of multivariate analysis of PFS in sorafenib-treated patients in whom lenvatinib treatment failed using the Cox proportional hazard regression model. According to this analysis, Child-Pugh class B significantly contributed to shorter PFS. The most common adverse events during sorafenib treatment were increased aspartate aminotransferase (AST) (58.5%), hypertension (49.1%), hypoalbuminemia (47.2%), proteinuria (37.7%), and fatigue (30.2%) (Table 6). The most common grade 3 or higher adverse events were increased AST (11.3%) and proteinuria (11.3%). Up to the date of data cutoff, 48 patients discontinued sorafenib treatment, of which 26 had confirmed radiological progression before discontinuing sorafenib. The most common causes of sorafenib discontinuation in patients without radiological progression were disorder of the physical status (5 patients, 10.4%), clinically determined disease progression which was assessed by tumor makers (5 patients, 10.4%), and proteinuria (3 patients, 6.3%). Of 35 patients who discontinued lenvatinib because of radiological progression, 20 patients discontinued sorafenib because of radiological progression and 4 patients discontinued sorafenib because of adverse events (proteinuria: 2 patients, disorder of physical status: 2 patients). Of the remaining 18 patients without radiological progression in whom lenvatinib treatment failed, 9 patients discontinued lenvatinib because of clinically determined disease progression and adverse events, respectively. Of the 9 patients who migrated to sorafenib after discontinuation of lenvatinib because of adverse events, 4 patients continued sorafenib until radiological progression. Reasons for discontinuing lenvatinib were increased AST, anorexia, gastrointestinal bleeding, and proteinuria. In the other 5 patients who discontinued both lenvatinib and sorafenib because of adverse events, the causes for lenvatinib discontinuation were fatigue (2 patients), rash, proteinuria, and stomati-

Table 4. Demographics and characteristics of lenvatinib-treated patients with advanced HCC who received sorafenib or regorafenib

Demographics/characteristics	Sorafenib (<i>n</i> = 53) (%)	Regorafenib (any lines) (<i>n</i> = 22) (%)	Regorafenib (third line) (<i>n</i> = 17) (%)
Sex, male	48 (90.6)	19 (86.4)	15 (88.2)
Age, >73 yr old	23 (43.4)	7 (31.8)	5 (29.4)
HBV positive	6 (11.3)	4 (18.2)	3 (17.6)
HCV positive	23 (43.4)	10 (45.5)	8 (47.1)
Alcohol abuse	15 (28.3)	4 (18.2)	2 (11.8)
Body weight, <60 kg	30 (56.6)	13 (59.1)	10 (58.8)
ECOG-PS, ≤1	53 (100.0)	22 (100.0)	17 (100.0)
Child-Pugh score			
5	16 (30.2)	8 (36.4)	6 (35.3)
6	20 (37.7)	9 (40.9)	6 (35.3)
≥7	17 (32.1)	5 (22.7)	5 (29.4)
Number of intrahepatic lesions, >7	32 (60.4)	15 (68.2)	12 (70.6)
Maximum size of intrahepatic lesions, >50 mm	23 (43.4)	11 (50.0)	9 (52.9)
Intrahepatic tumor occupation, ≥50%	4 (7.5)	3 (13.6)	3 (17.6)
MVI	16 (30.2)	6 (27.3)	5 (29.4)
EHM	21 (39.6)	12 (54.5)	10 (58.8)
BCLC stage C	36 (67.9)	15 (68.2)	12 (70.6)
AFP, >400 ng/mL	23 (43.4)	7 (31.8)	4 (23.5)
Causes for discontinuation of lenvatinib			
Radiological progression	39 (73.6)	19 (86.1)	14 (82.4)
Adverse events	10 (18.9)	2 (9.1)	2 (11.8)
Others	4 (7.5)	1 (4.5)	1 (5.9)
Treatment line			
2nd-line	53 (100.0)	5 (22.7)	0
3rd-line	0	17 (77.3)	17 (100.0)

HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group; PS, performance status; MVI, macrovascular invasion; EHM, extrahepatic metastasis; BCLC, Barcelona clinic liver cancer; AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; ECOG-PS, Eastern Cooperative Oncology Group Performance Status.

tis. Two of these patients discontinued sorafenib after experiencing the same adverse events as with lenvatinib (fatigue: 1 patient, rash: 1 patient).

Regorafenib after Discontinuation of Lenvatinib

Twenty-two patients received regorafenib after discontinuation of lenvatinib, as second-line therapy in 5 patients and as third-line therapy in 17 patients. The baseline characteristics at the time of regorafenib administration of all 22 patients who received regorafenib in any lines and 17 patients who received regorafenib after sorafenib (third-line) are shown in Table 4. The median PFS of patients receiving regorafenib in any lines and as third-line therapy was 3.2 months (95% CI, 1.5–4.9 months) and 3.8 months (95% CI, 1.1–6.5 months), respectively (Fig. 3b). The ORR and the DCR according to

mRECIST were 13.6 and 36.3% for therapy in any lines and 17.6 and 41.2% in third-line therapy, respectively. Among adverse events during regorafenib treatment, we observed high frequencies of increased AST (59.1%), proteinuria (54.6%), hypertension (45.6%), fatigue (40.9%), palmar-plantar erythrodysesthesia (36.4%), and hypoalbuminemia (36.4%) (Table 7). Up to the time of data cutoff, 18 patients discontinued regorafenib, of which 8 patients migrated to posttreatment (TACE, 4 patients; ramucirumab, 3 patients; other, 1 patient). Radiological progression was confirmed in 9 patients, and 9 patients discontinued regorafenib due to adverse events. The most common causes of discontinuation of regorafenib were liver dysfunction (2 patients), anorexia (2 patients), and clinically determined disease progression (2 patients).

Table 5. Cox regression analysis of the factors for PFS with sorafenib treatment after lenvatinib in patients with advanced HCC

Variables	Univariate analysis		<i>p</i> value	Multivariate analysis		<i>p</i> value
	hazard ratio	95% CI		hazard ratio	95% CI	
Sex, male	1.070	0.360–3.177	0.903			
Age, >73 yr old	0.975	0.452–2.103	0.949			
Child-Pugh class B	2.755	1.248–6.078	0.012	2.755	1.248–6.078	0.012
HBV positive	0.992	0.233–4.225	0.992			
HCV positive	1.333	0.610–2.911	0.471			
Intrahepatic tumor volume, >50%	2.380	0.549–10.313	0.247			
BCLC C	1.145	0.509–2.577	0.743			
Baseline AFP, >400 ng/mL	2.208	0.974–5.010	0.058			
Responder to lenvatinib	0.896	0.414–1.941	0.781			
Discontinued lenvatinib after radiological progression	1.819	0.758–4.367	0.181			
Treatment duration of lenvatinib, >4.9 mo	1.292	0.558–2.988	0.550			

HBV, hepatitis B virus; HCV, hepatitis C virus; BCLC, Barcelona clinic liver cancer; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; CI, confidence interval; PFS, progression-free survival.

Fig. 3. a PFS in patients receiving sorafenib after lenvatinib. **b** PFS in patients receiving regorafenib after lenvatinib in any lines (dotted line) and 3rd line (solid line). PFS, progression-free survival.

Discussion

The present study described the clinical outcomes of patients with advanced HCC who were treated with sorafenib or regorafenib after failure of lenvatinib treatment. PFS, ORR, and DCR in patients treated with sorafenib after lenvatinib were far from what would be expected in patients with advanced HCC treated with MTAs in current clinical practice. On the other hand, the effectiveness of

regorafenib after lenvatinib indicated that regorafenib could be a potential second-line agent after lenvatinib.

To the best of our knowledge, this study is the first to report rates of migration to posttreatments and postsystemic therapies after lenvatinib in patients with advanced HCC in real-world practice. According to the post hoc analysis from the phase III study (REFLECT study), 32.6% of patients with lenvatinib as a first-line agent received any anticancer medication during the follow-up period [23].

Table 6. Adverse events (>10%) during treatment with sorafenib after lenvatinib in patients with advanced HCC

Events	Sorafenib (n = 53)	
	any (%)	grade ≥ 3 (%)
Aspartate aminotransferase increased	31 (58.5)	6 (11.3)
Hypertension	26 (49.1)	1 (1.9)
Hypoalbuminemia	25 (47.2)	0
Proteinuria	20 (37.7)	6 (11.3)
Fatigue	16 (30.2)	0
Thrombocytopenia	15 (28.3)	1 (1.9)
Bilirubin increased	14 (26.4)	2 (3.8)
Hemolysis	14 (26.4)	1 (1.9)
Palmar-plantar erythrodysesthesia	13 (24.5)	1 (1.9)
Anorexia	13 (24.5)	0
Serum amylase increased	9 (17.0)	2 (3.8)
Diarrhea	7 (13.2)	1 (1.9)
Erythema multiform	6 (11.3)	2 (3.8)
Alopecia	4 (7.5)	0
Hypothyroidism	4 (7.5)	0
White blood cell count decreased	4 (7.5)	1 (1.9)
Encephalopathy	3 (5.7)	0

HCC, hepatocellular carcinoma.

Since that study was conducted at a time when second-line MTAs, such as regorafenib, cabozantinib, and ramucirumab were not approved in most countries, the migration rate was lower than those in our study. Hiraoka et al. reported that 43.8% of patients with confirmed radiological progression during lenvatinib treatment were eligible for postprogression treatment after lenvatinib [24]. This rate of eligibility for postprogression treatment was similar with our rates of migration to posttreatment in real-world practice in patients with advanced HCC who received lenvatinib as a the first-line agent, although Hiraoka et al. excluded Child-Pugh B patients and patients with ECOG-PS >1 at the time of lenvatinib administration and included patients who had received previous systemic therapies. Our results also indicated that patients who were able to move on to posttreatment after lenvatinib had better liver function than those who did not migrate to posttreatment (Table 3). We also found 4 independent factors that contributed to migration to posttreatment after lenvatinib (male, baseline AFP >400 ng/mL, responder to lenvatinib, and discontinued lenvatinib after radiological progression). Interestingly, none of the 4 factors were related to liver function deterioration individually at the time of lenvatinib failure (online suppl. Supplementary Table; see www.karger.com/doi/10.1159/000515552 for all online suppl. material). These results might suggest

that the 4 independent factors contributed to liver function deterioration at the time of lenvatinib failure in a complex manner. Of these 4 factors, the only 1 we can improve in clinical practice is to reduce discontinuation of lenvatinib because of adverse events and continue using it until radiological progression. However, only about half of our patients were able to continue lenvatinib until radiological progression. This rate is similar with that in the report of Hiraoka et al. [24]. Recently, physicians' skills at managing adverse events from sorafenib were reported to improve over time [25]. Both our study and that of Hiraoka et al. were based on patient populations immediately after the approval of lenvatinib in Japan. As physicians improve their understanding of the characteristics of lenvatinib from reports based on real-world practice [18–20, 26–28], their skills at managing adverse events from lenvatinib as well as sorafenib will improve, and the probability of continuing lenvatinib until radiological progression will increase. Moreover, deterioration of liver function and worsening physical condition (so-called performance status) at the time of previous treatment failure are 2 major factors that prohibit patients with advanced HCC from transitioning to other systemic therapy. Skillful managements of adverse events will lead to maintaining both the liver function and physical status until the end of lenvatinib treatment. Increasing the probability of continuing lenvatinib until radiological progression will lead to an increase in the rates of migration to posttreatment after lenvatinib in patients with advanced HCC.

We showed that patients who moved on to posttreatment after lenvatinib had a better prognosis than patients who received palliative care. The analysis from the REFLECT trial showed that OS of patients who received posttreatment after lenvatinib was 20.8 months [23]. Moreover, lenvatinib responders who received any subsequent anticancer medication had a median OS of 25.7 months [23]. Our study found that lenvatinib responders had a significantly high probability of migration to posttreatment after failure of lenvatinib treatment compared with nonresponders. The results of the REFLECT trial and our study suggest that survival may be prolonged by migrating to appropriate postsystemic therapy in responders to lenvatinib who are considered to have a good prognosis [29]. To maximize the potential of lenvatinib in patients with advanced HCC, we should hasten the development of treatment streams after failure of lenvatinib.

The present study found that PFS, ORR, and DCR of patients treated with sorafenib after lenvatinib were 1.8 months, 1.8%, and 20.8%, respectively. These clinical outcomes were even worse than those found in phase III

Table 7. Adverse events (>10%) during treatment with regorafenib after lenvatinib in patients with advanced HCC

Events	Regorafenib (any lines) (<i>n</i> = 22)		Regorafenib (third line) (<i>n</i> = 17)	
	any (%)	grade ≥3 (%)	any (%)	grade ≥3 (%)
Aspartate aminotransferase increased	13 (59.1)	2 (9.1)	11 (64.7)	2 (11.8)
Proteinuria	12 (54.6)	0	9 (52.9)	0
Hypertension	10 (45.6)	2 (9.1)	9 (52.9)	2 (11.8)
Fatigue	9 (40.9)	0	7 (41.2)	0
Palmar-plantar erythrodysesthesia	8 (36.4)	2 (9.1)	4 (23.5)	0
Hypoalbuminemia	8 (36.4)	0	8 (47.1)	0
Anorexia	7 (31.8)	0	6 (35.3)	0
Bilirubin increased	7 (31.8)	3 (13.6)	7 (41.2)	3 (17.6)
Diarrhea	6 (27.3)	1 (4.5)	4 (23.5)	1 (5.9)
Hypothyroidism	5 (22.7)	0	4 (23.5)	0
Anemia	5 (22.7)	0	5 (29.4)	0
Thrombocytopenia	5 (22.7)	2 (9.1)	5 (29.4)	2 (11.8)
Serum amylase increased	4 (18.2)	0	3 (17.6)	0
Weight loss	3 (13.6)	0	3 (17.6)	0

HCC, hepatocellular carcinoma.

studies of other second-line MTAs, such as regorafenib, ramucirumab, and cabozantinib [15, 16]. Although the majority of the patients in those 3 trials had experienced failure of sorafenib treatment and thus were not directly comparable to our patient population, the outcomes of patients in our study who were treated with sorafenib after failure of lenvatinib were not satisfactory. On the other hand, PFS, ORR, and DCR might be more clinically acceptable in patients treated with regorafenib after lenvatinib than in patients treated with sorafenib after lenvatinib. Based on the preclinical study, lenvatinib is known to have a stronger effect on the inhibition of VEGFR and fibroblast growth factor receptor than sorafenib and regorafenib [30]. Meanwhile, sorafenib and regorafenib block PDGFR and KIT strongly as compared with lenvatinib, and sorafenib and regorafenib, unlike lenvatinib, have an effect on RAS/RAF inhibition. Moreover, regorafenib has a distinct molecular target profile and has more potent pharmacological activity than sorafenib [31, 32]. These differences may be related to the clinical outcomes following lenvatinib therapy. At the present time, regorafenib is generally used for patients with advanced HCC after sorafenib in accordance with the eligibility criteria of the RESORCE trial. That is, regorafenib is indicated for patients with advanced HCC in whom sorafenib has failed and who have confirmed radiological progression during sorafenib treatment and are tolerant of sorafenib. Several studies found that only

about one-third of sorafenib-treated patients with advanced HCC were eligible for regorafenib [33–35]. Sequential therapy from sorafenib to regorafenib is an effective treatment stream in both clinical trials and real-world practice, when sorafenib is the first-line agent in patients with advanced HCC [36, 37]. Recently, Yoo et al. suggested that regorafenib has potential to be effective in patients with advanced HCC regardless of previous treatments [38]. Taken together with our findings, it may be time to abandon the concept that regorafenib should follow sorafenib in patients with failure of lenvatinib treatment. Further prospective clinical trials that investigate the safety and efficacy of regorafenib administered directly after lenvatinib are urgently required.

Regarding adverse events with both sorafenib and regorafenib after lenvatinib, proteinuria was notable (sorafenib: 37.7%, regorafenib: 54.6%). The incidence of proteinuria in the present cohort was markedly higher than in both clinical trials and real-world practice [4, 5, 13, 36, 39]. This might be related to the continuation of MTAs after lenvatinib, which are associated with a high incidence of proteinuria. Although the present cohort did not include a large number of patients, further validation of the safety of sequential treatment with MTAs in advanced HCC is necessary.

The results of IMbrave 150, a global phase III study that found that atezolizumab plus bevacizumab significantly prolonged OS compared with sorafenib in patients

with advanced HCC, have led to a major transition in the treatment of advanced HCC [21]. The standard first-line treatment of advanced HCC has been changing to atezolizumab plus bevacizumab. In other words, treatment is changing rapidly from “the era of multi-MTAs” to “the era of combination immune therapies.” Although the prognosis of advanced HCC will be much better, patients who have been administered atezolizumab plus bevacizumab will eventually become refractory to treatment. Since it is expected that MTAs will be used for treatment after atezolizumab plus bevacizumab, lenvatinib will continue to be the first-choice MTA agent in patients with advanced HCC. To improve the clinical outcomes of patients with advanced HCC, establishment of the appropriate treatment stream is urgently required.

The present study had several limitations. First, the study collected data retrospectively, and all treatment decisions were made by the treating physicians. Moreover, because the patients in this cohort were all Japanese and were treated under the Japanese social health-care insurance system, not all results may be replicated in other parts of the world. Global observation studies are needed to verify the safety and efficacy of a wide variety of sequential treatments in patients with advanced HCC, in an era where multiple agents can be used in various combinations as a result of rapid drug development.

In conclusion, sorafenib may not be a candidate for use as a posttreatment agent after lenvatinib, according to the results of the present study. Regorafenib has the potential to become an appropriate posttreatment agent after lenvatinib. Further clinical trials are required to investigate sequential therapy from lenvatinib to regorafenib in patients with advanced HCC. Two other MTAs, ramucirumab and cabozantinib, should also be tested as posttreatment agents after lenvatinib.

Acknowledgement

The authors would like to thank Enago (www.enago.jp) for the English language review.

Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee. And this research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. For this type of study, formal consent was not required.

Conflict of Interest Statement

Sadahisa Ogasawara received grant support from Eisai, Bayer, and Eli Lilly, advisory fees from Eisai, Bayer, MSD, AstraZeneca, and Eli Lilly, and honoraria from Eisai, Bayer, MSD, AstraZeneca, and Eli Lilly. Yoshihiko Ooka received honoraria from Eisai. Naoya Kato received grant support from Eisai, Bayer, Takeda, and Eli Lilly, advisory fees from Eisai, Bayer, and Eli Lilly, and honoraria from Eisai, Bayer, and Eli Lilly. The other authors have no conflicts of interest to declare.

Funding Sources

This research received no external funding.

Author Contributions

Conceptualization: Sadahisa Ogasawara; methodology: Sadahisa Ogasawara; formal analysis: Keisuke Koroki, Naoya Kanogawa, and Sadahisa Ogasawara; investigation: Keisuke Koroki, Naoya Kanogawa, Susumu Maruta, Sadahisa Ogasawara, Yotaro Iino, Masamichi Obu, Tomomi Okubo, Norio Itokawa, Takahiro Maeda, Masanori Inoue, Yuki Haga, Atsuyoshi Seki, Shinichiro Okabe, Yoshihiro Koma, Ryosaku Azemoto, Masanori Atsukawa, Ei Itobayashi, Kenji Ito, Nobuyuki Sugiura, Hideaki Mizumoto, Hidemi Unozawa, Terunao Iwanaga, Takafumi Sakuma, Naoto Fujita, Hiroaki Kanzaki, Kazufumi Kobayashi, Soichiro Kiyono, Masato Nakamura, Tomoko Saito, Takayuki Kondo, Eiichiro Suzuki, Yoshihiko Ooka, Shingo Nakamoto, Akinobu Tawada, and Tetsuhiro Chiba; data curation: Keisuke Koroki, Naoya Kanogawa, and Susumu Maruta; writing – original draft preparation: Keisuke Koroki and Naoya Kanogawa; writing – review and editing: Sadahisa Ogasawara; supervision: Makoto Arai, Tatsuo Kanda, Hitoshi Maruyama, Jun Kato, and Naoya Kato; project administration: Naoya Kato.

Clinical Trial Number

The Chiba University Research Ethics Committee approved this study (No. 2896).

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