



ORIGINAL RESEARCH

Clinical features of lenvatinib for unresectable hepatocellular carcinoma in real-world conditions: Multicenter analysis

Atsushi Hiraoka¹  | Takashi Kumada² | Kazuya Kariyama³ | Koichi Takaguchi⁴ | Masanori Atsukawa⁵ | Ei Itobayashi⁶ | Kunihiko Tsuji⁷ | Kazuto Tajiri⁸ | Masashi Hirooka⁹ | Noritomo Shimada¹⁰ | Hiroshi Shibata¹¹ | Toru Ishikawa¹² | Hironori Ochi¹³ | Toshifumi Tada² | Hidenori Toyoda²  | Kazuhiro Nouse³ | Akemi Tsutsui⁴ | Norio Itokawa⁵ | Michitaka Imai¹² | Kouji Joko¹³ | Yoichi Hiasa⁹ | Kojiro Michitaka¹ | **On behalf of the Real-life Practice Experts for HCC (RELPEC) Study Group, HCC 48 Group (hepatocellular carcinoma experts from 48 clinics in Japan)**

¹Gastroenterology Center, Ehime Prefectural Central Hospital, Matsuyama, Japan

²Department of Gastroenterology and Hepatology, Ogaki Municipal Hospital, Gifu, Japan

³Department of Gastroenterology, Okayama City Hospital, Okayama, Japan

⁴Department of Hepatology, Kagawa Prefectural Central Hospital, Takamatsu, Japan

⁵Division of Gastroenterology and Hepatology, Department of Internal Medicine, Nippon Medical School, Tokyo, Japan

⁶Department of Gastroenterology, Asahi General Hospital, Asahi, Japan

⁷Center of Gastroenterology, Teine Keijinkai Hospital, Sapporo, Japan

⁸Department of Gastroenterology, Toyama University Hospital, Toyama, Japan

⁹Department of Gastroenterology and Metabolism, Ehime University Graduate School of Medicine, Toon, Japan

¹⁰Division of Gastroenterology and Hepatology, Otakanomori Hospital, Kashiwa, Japan

¹¹Department of Gastroenterology, Tokushima Prefectural Central Hospital, Tokushima, Japan

¹²Department of Gastroenterology, Saiseikai Niigata Daini Hospital, Niigata, Japan

¹³Hepato-biliary Center, Matsuyama Red Cross Hospital, Matsuyama, Japan

Correspondence

Atsushi Hiraoka, Gastroenterology Center, Ehime Prefectural Central Hospital, Matsuyama, Japan.
Email: hirage@m.ehime-u.ac.jp

Abstract

Background/Aim: Presently, there are no therapeutic options for unresectable hepatocellular carcinoma (u-HCC) patients who are intolerant to sorafenib or regorafenib failure. There have been no reports with detailed clinical findings of lenvatinib (LEN), a newly developed first-line tyrosine kinase inhibitor (TKI), obtained in real-world practice. We aimed to elucidate the therapeutic efficacy of LEN.

Materials/Methods: From March to August 2018, 105 u-HCC patients were treated with LEN. Following exclusion of those who started with a reduced LEN dose and/or had a short observation period (<2 weeks), 77 patients (72.0 ± 8.9 years, 59 males, 8 mg/12 mg = 49/28, Liver Cancer Study Group of Japan 6th [LCSGJ]-TNM

stage II/III/IVa/IVb = 8/28/4/37, and American Joint Committee on Cancer/Union for International Cancer Control 8th [AJCC/UICC]-TNM stage IB:II:IIIA:IIIB:IVA:IVB = 2:27:6:5:9:28) were divided into two groups (TKI naïve [$n = 33$] and TKI experienced [$n = 44$], including 11 with regorafenib history). Therapeutic response was evaluated using mRECIST. Clinical data were retrospectively evaluated.

Results: There were significant differences in age (74.6 ± 11.2 vs 70.0 ± 5.9 years, $P = 0.040$), LCSGJ-TNM (II:III:IVa:IVb = 8:12:1:12 vs 0:16:3:25, $P = 0.006$), and AJCC/UICC-TNM (IB:II:IIIA:IIIB:IVA:IVB = 2:17:1:1:4:8 vs 0:10:5:4:5:20, $P = 0.028$), while hepatic reserve function, adverse event (AE) profiles, and progression-free survival (89.7%/80.4% vs 90.5%/80.1%, $P = 0.499$) and overall survival (96.7%/96.7% vs 100%/92.3%, $P = 0.769$) after 4 and 12 weeks were not significantly different between the TKI-naïve and TKI-experienced groups. Overall response rate and disease control rate at 4 weeks ($n = 52$) were 38.5% and 80.8%, respectively, and 32.4% and 70.3%, respectively, at 12 weeks ($n = 37$). A significant decline in log₁₀ AFP from the baseline to 4 weeks after introducing LEN was observed in patients with PR and SD (2.047 ± 1.148 vs 1.796 ± 1.179 , $P < 0.001$).

Conclusion: Regardless of past TKI therapy, therapeutic response and AEs after introducing LEN were similar. LEN may be an important treatment for the present unmet need regarding TKI treatment against u-HCC.

KEYWORDS

adverse event, albumin-bilirubin grade, alpha-fetoprotein, hand-foot skin reaction, hepatocellular carcinoma, lenvatinib, muscle volume, regorafenib, sorafenib

1 | INTRODUCTION

For treatment of unresectable hepatocellular carcinoma (u-HCC), tyrosine kinase inhibitors (TKIs), such as sorafenib (SOR)^{1,2} and regorafenib (REG),^{3,4} have been introduced. SOR was developed as a first-line agent for u-HCC, while REG is used as second-line therapy in patients who show good tolerability and progressive disease (PD) with SOR. Recently, lenvatinib (LEN), a new TKI,^{5,6} has become available as a first-line drug for u-HCC. However, though the number of TKIs for u-HCC has increased, there is presently no therapeutic option for patients with SOR failure or who show intolerability for SOR as well as failure with REG, indicating an important and practical unmet need. Following the introduction of LEN in clinical practice in Japan in March 2018, the drug has been used in real-world practice not only for TKI-naïve but also for TKI-experienced patients as second- or third-line treatment.⁷ On the other hand, therapeutic response and adverse events (AEs) associated with LEN treatment for u-HCC patients with and without a past history of TKI have not been elucidated. In the present study, we analyzed clinical features of patients who received LEN treatment for u-HCC for therapeutic response and AEs.

2 | MATERIALS AND METHODS

From March to August 2018, LEN (Lenvima[®], Eisai Co., Ltd., Tokyo, Japan) was given to 105 u-HCC Japanese patients receiving treatment at 13 different institutions in Japan (Ehime Prefectural Central Hospital [$n = 19$], Okayama City Hospital [$n = 12$], Kagawa Prefectural Central Hospital [$n = 12$], Nippon Medical School Hospital [$n = 12$], Asahi General Hospital [$n = 10$], Teine Keijinkai Hospital [$n = 7$], Ogaki Municipal Hospital [$n = 6$], Toyama University Hospital [$n = 6$], Ehime University Hospital [$n = 6$], Otakanomori Hospital [$n = 5$], Tokushima Prefectural Central Hospital [$n = 4$], Saiseikai Niigata Daini Hospital [$n = 3$], Matsuyama Red Cross Hospital [$n = 3$]). We retrospectively examined the records of those patients and collected clinical data obtained at the introduction of LEN, as well as after 2 weeks and every 4 weeks thereafter. Following exclusion of those who started with a reduced LEN dose and/or had a short observation period (<2 weeks), 77 patients were enrolled and divided into two groups, TKI naïve ($n = 33$) and TKI experienced ($n = 44$), according to their past history with TKI treatments. Flow diagram of enrolled patients is shown in Figure 1. Clinical characteristics, therapeutic response

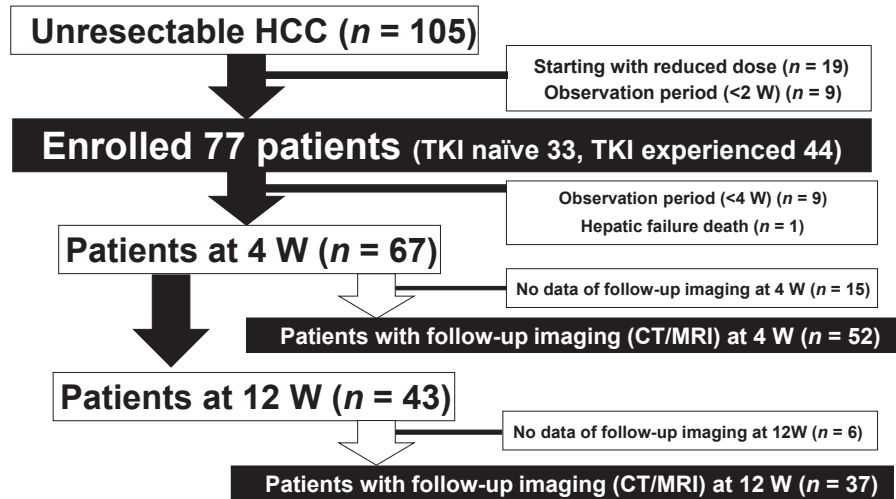


FIGURE 1 Flow diagram of enrolled patients. HCC, hepatocellular carcinoma; TKI, tyrosine kinase inhibitor; W, weeks

including progression-free survival rate (PFSR) and overall survival rate (OSR), and AEs were analyzed in a retrospective manner.

Patients positive for anti-hepatitis C virus (HCV) were judged to have HCC due to HCV, while those positive for hepatitis B virus surface antigen (HBsAg) were judged to have HCC due to hepatitis B virus (HBV).

2.1 | Assessment of hepatic reserve function and prognosis.

Child-Pugh classification⁸ and ALBI grade were used to assess hepatic reserve function. ALBI grade was calculated based on serum albumin and total bilirubin values using the following formula: $[\text{ALBI score} = (\log_{10} \text{bilirubin } (\mu\text{mol/L}) \times 0.66) + (\text{albumin } (\text{g/L}) \times -0.085)]$, and defined by the following scores: $\leq -2.60 = \text{Grade 1}$, > -2.60 to $\leq -1.39 = \text{Grade 2}$, $> -1.39 = \text{Grade 3}$.^{9,10} For a more detailed evaluation of the middle grade of ALBI (grade 2), we used a modified ALBI (mALBI) grade by creating 4 grades, including sub-grading for the middle grade (2a and 2b), with an ALBI score of -2.270 , which was reported as the cutoff value for indocyanine green retention 15 minutes 30%, used as the value for dividing 2a and 2b.^{12,13}

2.2 | Assessment of muscle volume

Muscle volume loss (MVL) was determined using the following previously reported index: [psoas index (PI): bilateral psoas muscle area of middle L3 level (cm^2)/height (m)²; cutoff values for MVL of males = $4.24 \text{ cm}^2/\text{m}^2$, females = $2.50 \text{ cm}^2/\text{m}^2$], based on CT findings.¹⁴ PI was manually calculated using psoas muscle area at the middle L3 level in CT findings with personal computer software (Centricity Web DX ver.3.7.3.6417: GE Healthcare Japan, Tokyo, Japan, or OsiriX DICOM Viewer MD 9.5: <https://www.osirix-viewer.com>). Muscle volume was calculated using computed

tomography (CT) findings obtained at the start of LEN and again after 4 and 12 weeks in patients for whom CT imaging data were available.

2.3 | Diagnosis and treatment of HCC

HCC was diagnosed based on an increasing course of alpha-fetoprotein (AFP), as well as dynamic CT,¹⁵ magnetic resonance imaging (MRI),^{16,17} contrast-enhanced ultrasonography (CEUS) with perflubutane (Sonazoid®, Daiichi Sankyo Co., Ltd. Tokyo, Japan),^{18,19} and/or pathological findings. American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor node metastasis (TNM) stage was used for evaluation of tumor progression as well as TNM stage, which was determined as previously reported in studies for staging of HCC conducted by the Liver Cancer Study Group of Japan (LCSGJ).²⁰ The present study protocol was approved by the Institutional Ethics Committee of Ehime Prefectural Central Hospital (No. 29-75).

2.4 | LEN treatment and assessment of AEs

After obtaining written informed consent, LEN was orally administered at 8 mg/d to patients weighing $<60 \text{ kg}$ and 12 mg/d to those $\geq 60 \text{ kg}$, and discontinued when any unacceptable or serious AE or clinical tumor progression was observed. According to the guidelines for administration of LEN, the drug dose should be reduced or treatment interrupted when a patient develops any grade 3 or more severe AE or if any unacceptable grade 2 drug-related AE occurs. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.²¹ The worst grade for each AE during the present observation period was recorded. If a drug-related AE occurred, dose reduction or temporary interruption was maintained until the symptom was resolved to grade 1 or 2, according to the guidelines provided by the manufacturer.

2.5 | Evaluation of therapeutic response

Local physicians at each institution evaluated tumors using enhanced CT or MRI results obtained at 4, 8, or 12 weeks after introducing LEN, in accordance with the modified RECIST guidelines.^{22,23}

2.6 | Statistical analysis

Data are expressed as the mean and standard deviation (SD). Statistical analyses were performed using Welch's *t* test, Fischer's exact test, Mann-Whitney's *U* test, a paired *t* test, Wilcoxon signed-rank test, Kaplan-Meier method, and a

TABLE 1 Characteristics of patients without a reduced lenvatinib dose starting and with observation period more than 2 wk

	All (n = 77)	TKI naïve (n = 33)	TKI experienced (n = 44)	P value
Age (y)	72.0 ± 8.9	74.6 ± 11.2	70.0 ± 5.9	0.040
Gender (male:female)	59:18	26:7	33:11	0.705
BMI (kg/m ²)	22.2 ± 4.2	22.6 ± 3.4	21.9 ± 4.8	0.439
ECOG PS (0:1:2)	67:8:2	28:4:1	39:4:1	0.634
Etiology (HCV:HBV:alcohol:others)	38:14:12:13	14:6:5:8	24:8:7:5	0.188
AST (IU/L)	57.2 ± 67.7	48.8 ± 26.0	63.6 ± 86.6	0.289
ALT (IU/L)	43.9 ± 50.3	42.7 ± 36.3	44.8 ± 59.2	0.853
Platelets (×10 ⁴ /μL)	14.7 ± 5.5	14.1 ± 5.8	15.1 ± 5.4	0.434
Total bilirubin (mg/dL)	0.8 ± 0.4	0.8 ± 0.3	0.9 ± 0.5	0.732
Albumin (g/dL)	3.6 ± 0.5	3.6 ± 0.5	3.6 ± 0.5	0.498
Prothrombin time (%)	90.6 ± 13.3	89.9 ± 13.5	91.2 ± 13.3	0.673
Child-Pugh score (5:6:7:8)	42:25:9:1	19:11:3:0	23:14:6:1	0.512
ALBI grade (1:2:3)	26:49:2	11:21:1	15:28:1	0.917
[mALBI grade (1:2a:2b:3)]	[26:19:30:2]	[11:7:14:1]	[15:12:16:1]	0.690
(ALBI score)	(−2.32 ± 0.49)	(−2.36 ± 0.49)	(−2.30 ± 0.49)	0.577
AFP (ng/mL)	3248.2 ± 15406.1	2515.9 ± 8252.5	3797.4 ± 19185.9	0.693
Intrahepatic tumor size (cm)	4.1 ± 4.5	2.8 ± 2.3	5.1 ± 5.5	0.019
Number of intrahepatic tumors (none:single:multiple)	9:4:64	5:3:25	4:1:39	0.326
TNM stage, AJCC/UICC 8th (IB:II:IIIA:IIIB:IVA:IVB)	2:27:6:5:9:28	2:17:1:1:4:8	0:10:5:4:5:20	0.028
TNM stage, LCSGJ 6th (II:III:IV) [IVa:IVb]	8:28:41 [4:37]	8:12:13 [1:12]	0:16:28 [3:25]	0.006
Positive for MVI (Vp1:Vp2:Vp3:Vp4:Vv1:Vv2:Vv3) ^a	17 (22.1%) (2:5:4:3:1:2:4)	2 (6.1%) (0:1:1:0:0:0)	15 (34.1%) (2:4:3:3:1:2:4)	0.005
Positive for EHM (lung:LN:bone:peritoneum:adrenal gland:others) ^a	37 (48.1%) 11:15:9:5:2:2	12 (36.4%) (1:5:1:4:0:2)	25 (56.8%) (10:10:8:1:2:0)	0.107
naïve:recurrence	2:75 (median number of past treatments 5)	2:31	0:44	0.180
Past history of hypertension	33 (42.9%)	9(27.3%)	24 (54.5%)	0.021
Past history of diabetes mellitus	21 (27.3%)	11 (33.3%)	10 (22.7%)	0.316
Past history of SOR and REG	44 (57.1%)	—	11 (14.4%) (REG)	—
Initial dose of LEN (8:12 mg/d)	49:28	22:11	27:17	0.811
Average observation period after starting LEN (d)	79.3 ± 40.7	67.1 ± 41.9	88.4 ± 37.7	0.025

AFP, alpha-fetoprotein; AJCC/UICC 8th, American Joint Committee on Cancer/Union for International Cancer Control, 8th edition; ALBI grade, albumin-bilirubin grade; ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; EHM, extra-hepatic metastasis; HBV, hepatitis B virus; HCV, hepatitis C virus; LCSGJ 6th, the Liver Cancer Study Group of Japan, 6th edition; LEN, lenvatinib; LN, lymph node; MVI, major venous invasion; REG, regorafenib; SOR, sorafenib; TNM stage, tumor node metastasis stage.

^aOverlapping cases.

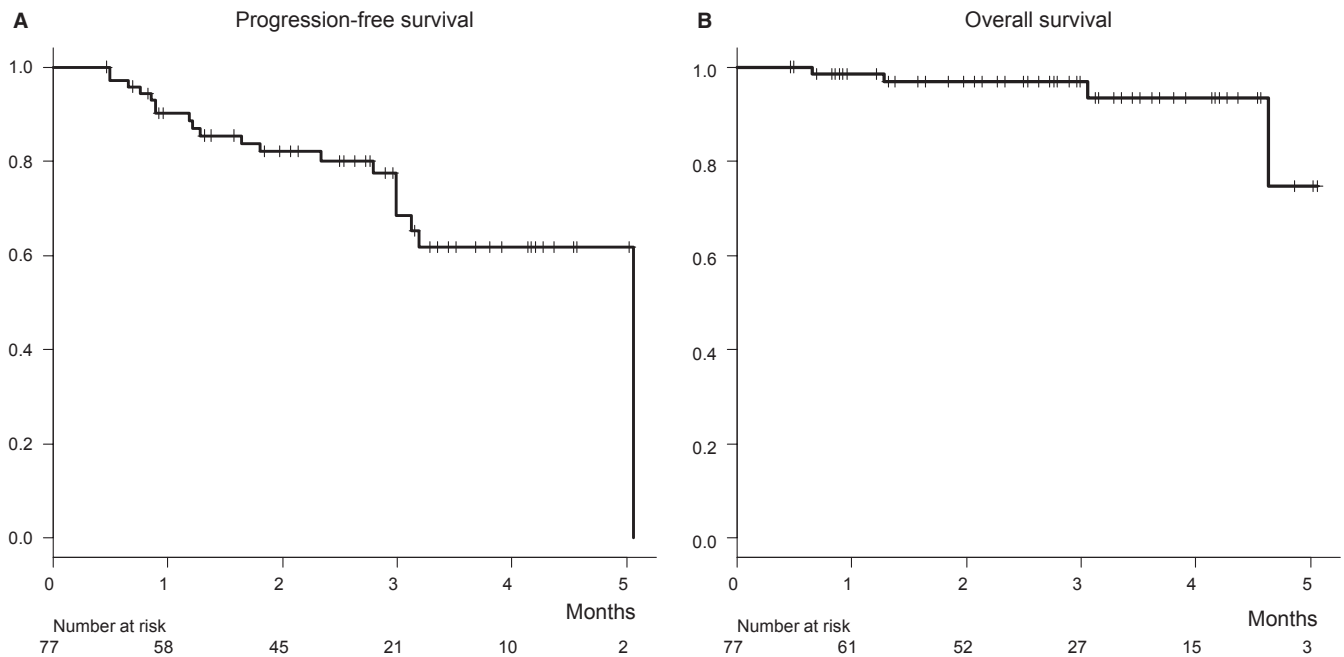


FIGURE 2 Progression-free and overall survivals. After 4, 8, and 12 wk of treatment, the progression-free survival rate (PFSR) was 90.1%, 82.1%, and 80.1%, respectively (A), while overall survival rate (OSR) was 98.6%, 96.9%, and 93.4%, respectively (B)

log-rank test. A *P* value less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed using Easy R (EZR), version 1.29 (Saitama Medical Center, Jichi Medical University, Saitama, Japan),²⁴ a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

Following exclusion of patients whose initial LEN dose was reduced or those with a short observation period <2 weeks, a total of 77 were analyzed and their characteristics are shown in Table 1. The average observation period for all subjects after introduction of LEN was 79.3 ± 40.7 days. Forty-four (57.1%) had a past history of SOR treatment (TKI-experienced group), including 11 (14.4%) who were also treated with REG as second-line therapy.

The first evaluation of the therapeutic effect of LEN using an imaging modality was performed in 52 patients at 4 weeks after introduction of the drug. Complete response (CR) was noted in none, partial response (PR) in 20, stable disease (SD) in 22, and PD in 10 (overall response rate [ORR]: 38.5%, disease control rate [DCR]: 80.8%). In results of CT/MRI imaging of 37 patients evaluated at 12 weeks, CR was noted in 1, PR in 11, SD in 14, and PD in 11 (ORR: 32.4% and DCR: 70.3%). At 4, 8, and 12 weeks, PFSR was 90.1%, 82.1%, and 80.1%, respectively (Figure 2A), while OSR was 98.6%, 96.9%, and 93.4%, respectively (Figure 2B). Although older age, shorter observation period, lower frequency of past

history of hypertension, and reduced tumor burden shown by lower TNM stage with both systems were noted in the TKI-naïve group as compared to the experienced group, there were no significant differences between them in regard to clinical characteristics, especially hepatic reserve function (Child-Pugh score, ALBI score/grade, mALBI grade) (Table 1). As a result, PFSR and OSR at 4, 8, and 12 weeks were not significantly different between the TKI-naïve and TKI-experienced groups (PFSR: naïve group, 89.7%, 80.4%, 80.4% vs experienced group, 90.5%, 83.0%, 80.1%, respectively, *P* = 0.499; OSR: 96.7%, 96.7%, 96.7% vs 100%, 97.4%, 92.3%, respectively, *P* = 0.769) (Figure 3A,B). A significant decline in log₁₀ AFP from the baseline to 4 weeks after introducing LEN was observed in all patients who obtained disease control (PR:SD = 20:22) (baseline vs 4 weeks: 2.047 ± 1.148 vs 1.796 ± 1.179 , *P* < 0.001). After exclusion of those with normal AFP level (<10 ng/mL) (*n* = 13), the significant relative decline remained (baseline vs 4 weeks: 2.662 ± 0.798 vs 2.393 ± 0.946 , *P* = 0.002) (*n* = 29).

After starting LEN treatment, patients with Child-Pugh class A had worsened to Child-Pugh B or C in 23.4% of patients at 4 (*P* < 0.001) and in 23.7% at 12 weeks (*P* = 0.002) (Figure 4). Furthermore, a significant decline in ALBI score from the baseline (-2.32 ± 0.49) was observed at 4 (-2.18 ± 0.54 [*n* = 67], *P* < 0.001) and 12 (-2.10 ± 0.55 [*n* = 43], *P* < 0.001) weeks after the start of LEN treatment. AEs that occurred following the start of LEN in these patients are presented in Table 2. HFSR was the most common in the present cohort (all grades: *n* = 31 [40.3%], grade 3: *n* = 7 [9.1%]), followed by general fatigue (grades 1/2: *n* = 26 [33.8%]), appetite loss (all grades:

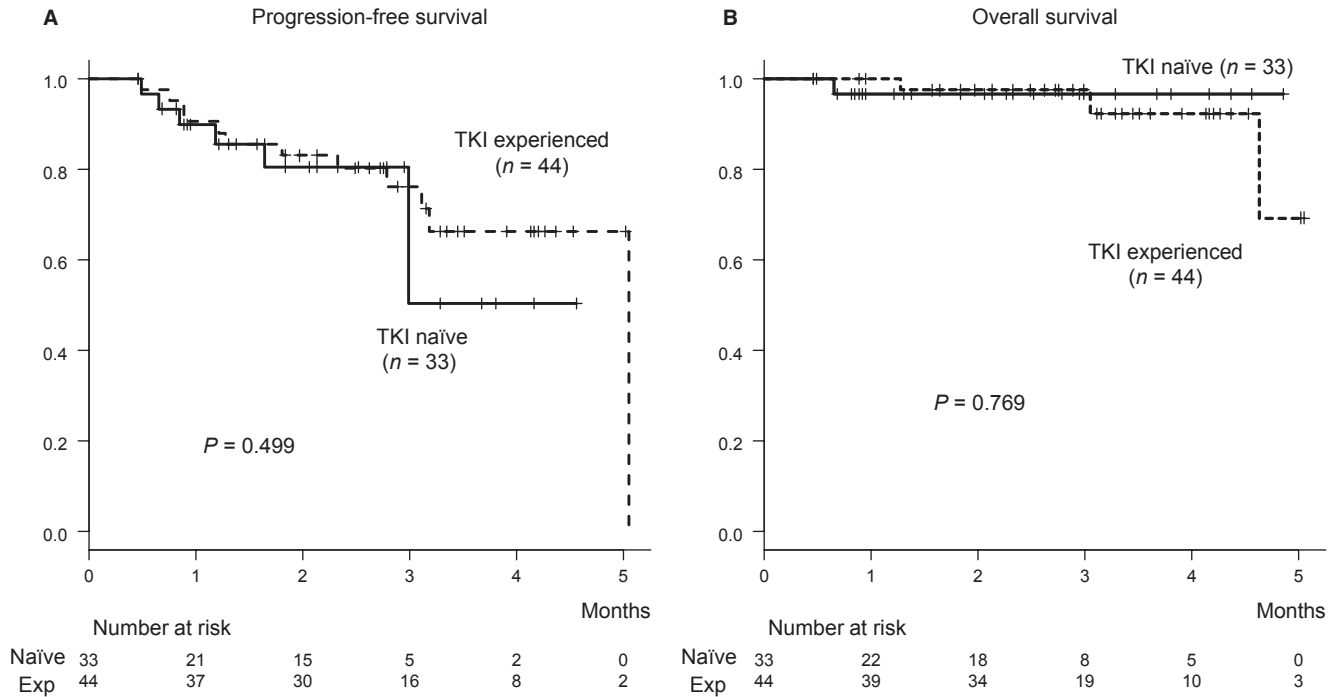


FIGURE 3 Progression-free and overall survivals for tyrosine kinase inhibitor-naïve and TKI-experienced groups. After 4, 8, and 12 wk of treatment, the progression-free survival rate (PFSR) and overall survival (OSR) were not significantly different between the tyrosine kinase inhibitor (TKI)-naïve (solid line) and TKI-experienced groups (broken line) (PFSR: 89.7%/80.4%/80.4% vs 90.5%/83.0%/80.1%, $P = 0.499$; OSR: 96.7%/96.7%/96.7% vs 100%/97.4%/92.3%, $P = 0.769$)

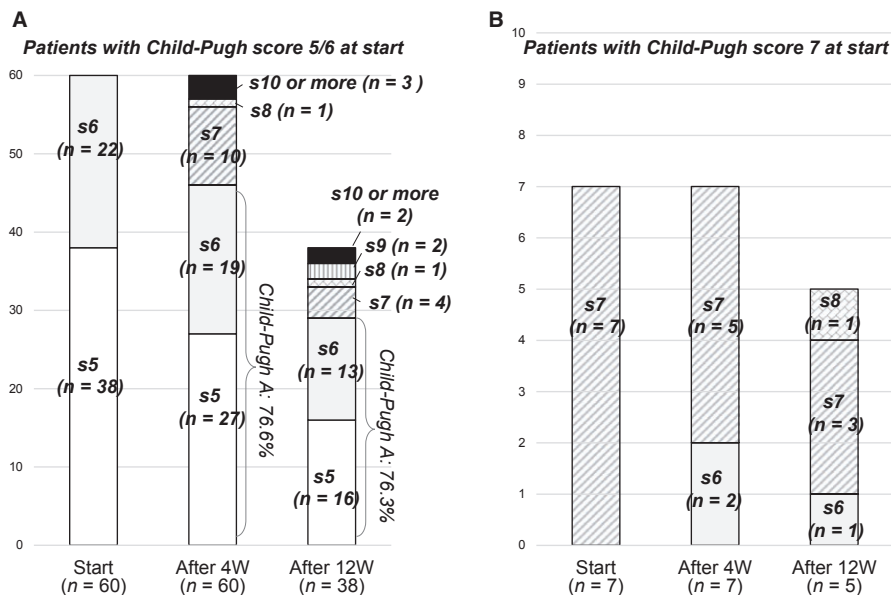


FIGURE 4 Child-Pugh score at start, then 4 and 12 weeks after introducing lenvatinib. After starting LEN treatment, Child-Pugh class A had worsened to Child-Pugh B or C 23.4% patients at 4 wk ($P < 0.001$) and 23.7% at 12 wk ($P = 0.002$)

$n = 22$ [28.6%], grade 3: $n = 5$ [6.5%], hoarseness (all grades: $n = 17$ [22.1%], grade 3: none), and hypothyroidism (all grades: $n = 15$ [19.5%], grade 3: none). In 3 (3.9%) patients, destructive thyroiditis was observed (grade 2, $n = 1$; grade 3, $n = 2$).²⁵ Although there was no significant relative change in regard to the level of FT4 (baseline vs 4 weeks: 2.0 ± 4.1 vs 1.1 ± 0.5 ng/dL, $P = 0.107$), TSH level was significantly elevated from the baseline after the first 4 weeks of LEN

treatment (baseline vs 4 weeks: 5.9 ± 12.5 vs 15.2 ± 29.7 μ IU/mL, $P = 0.003$). Also, the levels of NH₃, serum amylase, and estimated glomerular filtration rate (eGFR) did not show significant changes within the first 4 weeks (NH₃: 47.7 ± 27.1 vs 47.9 ± 32.7 μ g/dL, $P = 0.548$; serum amylase: 88.6 ± 38.4 vs 101.1 ± 19.9 U/L, $P = 0.809$; eGFR: 75.7 ± 19.6 vs 73.0 vs 21.2 mL/min/1.73 m², $P = 0.279$). Among 45 patients who experienced down-dosing or a pause in LEN treatment due to

TABLE 2 Adverse events of lenvatinib treatment

	All patients (n = 77)			TKI naïve (n = 33)		TKI experienced (n = 44)		P value
	G1/2	G3/4	Any grade (%)	G1/2	G3/4	G1/2	G3/4	
HFSR ^a	24	7	31 (40.3)	6/4	1/0	6/8	6/0	0.288
General fatigue ^a	26	—	26 (33.8)	3/6	—	7/8	—	0.727
Appetite loss ^a	17	5	22 (28.6)	1/4	2/0	6/6	3/0	0.451
Hoarseness ^a	17	0	17 (22.1)	9/2	0/—	5/1	0/—	0.104
Hypothyroidism ^a	15	0	15 (19.5)	2/4	0/0	0/9	0/0	0.199
Destructive thyroiditis ^a	1	2	3 (3.9)	0/0	1/0	0/1	1/0	1.000
Hypertension ^a	9	5	14 (18.2)	2/3	2/0	0/4	3/0	0.825
Diarrhea ^a	12	1	13 (16.7)	2/2	0/0	6/2	1/0	0.735
Urine protein ^a	8	3	11 (14.3)	1/3	2/—	2/2	1/—	0.675
Hyperammonemia/hepatic coma ^a	3	2	5 (6.5)	1/1	1/0	0/1	1/0	0.788
Fever within 2 wk ^a	2	1	3 (3.9)	0/0	0/0	1/1	1/0	0.132
Others ^a	24	9	33	2/2	5/1 ^b	13/7	3/0	

G, grade; HFSR, hand-foot skin reaction; TKI, tyrosine kinase inhibitor; —: no setting for the applicable grade in the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

^aSome events are overlapped.

^bCase of hypoglycemia due to appetite loss.

an AE during the present observation period, LEN was abandoned in 17 (PD, n = 5; AEs, n = 12). The median period to initial dose reduction or pause of LEN was 40 days. Of 8 with an HFSR with a grade of 3 in previous treatments with a TKI, 87.5% also had an HFSR (grade 3, 2, 1; n = 2, 3, 2, respectively) with LEN treatment, while 44.4% of 18 with an HFSR with a grade of 2 during previous TKI treatments had an HFSR with LEN (grade 3, 2, 1; n = 3, 3, 2, respectively) (Figure 5).

The data of CT imaging findings at introducing LEN were obtained for 51 patients, of whom 18 (35.3%) had MVL. As a sub-analysis, relative changes in muscle volume at 4 and 12 weeks after introducing LEN were evaluated in 41 and 25 patients, respectively, whose data of CT imaging findings obtained at the start of and approximately 4 and 12 weeks after beginning treatment. In those, the relative change in PI with total psoas muscle area at L3 level in the 41 patients after 4 weeks was $-0.210 \pm 0.315 \text{ cm}^2/\text{m}^2$, while that in the 25 patients after 12 weeks was $-0.275 \pm 0.372 \text{ cm}^2/\text{m}^2$.

4 | DISCUSSION

Development of TKI treatment for u-HCC has improved the prognosis of affected patients. Following the introduction of SOR, global trials of sunitinib,²⁶ brivanib,²⁷ linifanib,²⁸ and erlotinib plus SOR²⁹ were conducted, though none of those drugs showed superiority and each of the trials ended in failure. Thus, there was no additional first- or second-line TKI treatment for u-HCC developed until the introductions of

REG^{3,4} and LEN.⁶ Recently, REG was developed as a second-line option for SOR in patients who met the RESORCE trial criteria,³ after which LEN became available as a first-line oral TKI targeting VEGF receptors 1-4, PDGF receptor α , RET, and KIT.⁶

In the present study, early therapeutic response with LEN was favorable and patients obtained disease control within 4 weeks, as follow-up imaging showed a significant decline in log₁₀ AFP from the baseline. Kuzuya et al³⁰ have reported that a decreased AFP ratio from the baseline at 4 weeks after introduction of SOR was a predictor of good therapeutic response (PR, SD). Thus, a decline of log₁₀ AFP from the baseline within the first 4 weeks might also have predictive value for therapeutic response in patients receiving LEN treatment. In addition, a previous study noted that fever within 2 weeks after the start of SOR therapy may be useful as a predictor of favorable treatment response in patients with advanced HCC and receiving SOR treatment.³¹ Three of our patients developed a fever within 2 weeks after the start of LEN (grade 1, 2, 3: each 1 patient), in whom therapeutic response was PD in 2 and SD in 1. It would be important to examine the clinical importance of fever in patients receiving LEN therapy as a useful predictor of a favorable treatment response in a future study with a larger number of patients.

Not all patients treated with SOR in clinical practice meet the RESORCE trial criteria; thus, the frequency of u-HCC patients indicated for REG has been reported to only range from 30.6% to 37.0% of those confirmed by radiological

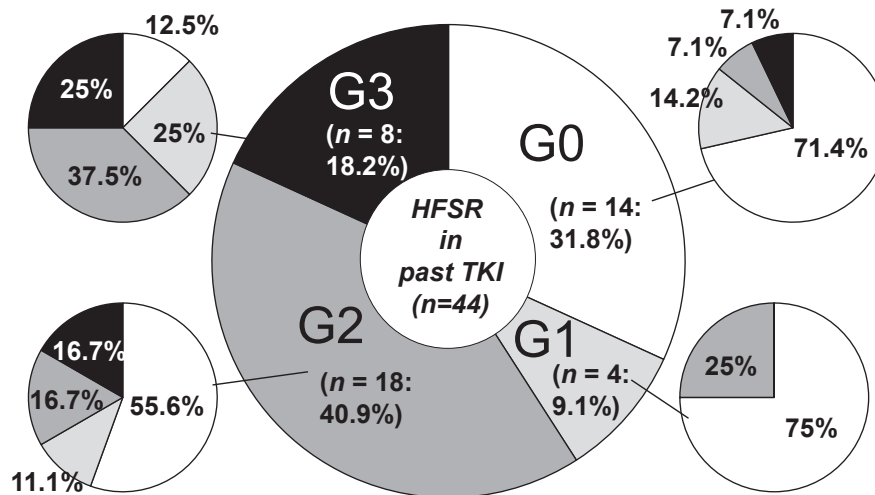


FIGURE 5 Hand-foot skin reaction occurrence in tyrosine kinase inhibitor-experienced group. Of 8 patients who had undergone past tyrosine kinase inhibitor (TKI) treatments and developed a grade 3 hand-foot skin reaction (HFSR), 87.5% had an HFSR with lenvatinib (LEN) therapy (G3, 2, 1; n = 2, 3, 2, respectively). Furthermore of 18 with a grade 2 HFSR in past TKI treatments, 44.4% had an HFSR with LEN (G3, 2, 1; n = 3, 3, 2, respectively). Of 4 with a grade 1 HFSR in previous TKI treatments, grade 2 occurred in 1 and no HFSR was seen in 3 with LEN treatment. In 14 without an HFSR in past TKI treatments, 28.6% developed HFSR with LEN treatment (G3, 2, 1; n = 3, 3, 2, respectively)

findings to have PD with SOR therapy.^{32,33} Absence of a therapeutic option for second-line treatment after SOR other than REG in u-HCC patients who do not meet the RESORCE trial eligibility criteria (tolerability for SOR) is an important clinical issue. Our previous study examined the use of LEN for u-HCC in both TKI-naïve and TKI-experienced patients in real-world clinical situations in Japan,⁷ as accurate determination of clinical profile differences including detailed therapeutic response and AE occurrence between TKI-naïve and TKI-experienced patients has become an urgent clinical issue. In the present results, PFSR and OSR were not significantly different between the TKI-naïve and TKI-experienced groups, and similar AE profiles were observed in both. We consider that LEN may have potential to satisfy the unmet need of clinical TKI treatment for u-HCC. On the other hand, the cohort in this retrospective study included u-HCC patients classified as Child-Pugh B and/or with major vein tumor thrombosis. However, indication for LEN treatment in such patients should be determined with caution, because no evidence has been presented showing the safety or effects of LEN in u-HCC patients classified as Child-Pugh B and/or with major vein tumor thrombosis.

In the REFLECT trial reported by Kudo,⁶ the frequency of HFSR was less in patients that received SOR (all grades: 26.9% vs 52.4%), whereas all grades of HFSR were observed more frequently in the present analysis (40.3%). Although there was no statistical difference in the frequency of HFSR between our TKI-naïve and TKI-experienced groups (33.3% vs 45.5%, $P = 0.350$), past history of high-grade HFSR might be an important risk factor of it developing during LEN therapy. Thus, HFSR should be kept in mind as a commonly occurring AE in patients with a history of that condition during

previous SOR and/or REG treatments. HFSR in association with SOR has been reported as a factor predicting a better therapeutic effect of SOR for HCC.^{36,37} Based on these findings, the relationship between HFSR and therapeutic response with LEN treatment should be analyzed in the future. Nevertheless, countermeasures against HFSR are most important for patients with a past history of HFSR in order to maintain TKI adherence for enhancing the anti-cancer effect.

In the present cohort, Child-Pugh class and ALBI score became worse at 4 and 12 weeks after starting LEN treatment. In addition to HFSR, general fatigue and appetite loss were the second and third most frequent AEs seen in the present analysis, and it is thought that LEN and these AEs have direct effects on liver function and nutritional status. To maintain adherence to LEN therapy, it is important not only to monitor and treat as carefully as possible AEs but also to keep in mind to introduce LEN, as well as SOR, as possible as in better liver function, if necessary for LEN treatment.

HCC is often seen in patients with chronic liver disease (CLD). Additionally, MVL is not rare in affected patients¹⁴ and its frequency was shown to increase in association with the progression of CLD stage.³⁸ Moreover, it has been reported that MVL is a more significant prognostic factor than portal hypertension in liver cirrhosis (LC) patients (Child-Pugh class A/B),³⁹ and also an important prognostic factor following not only surgical resection⁴⁰ but also SOR treatment⁴¹ in patients with HCC. Recently, a meta-analysis study reported that MVL was a prognostic factor regardless of therapeutic modality given for HCC by Chang et al.⁴² Furthermore, in addition to LC and HCC, muscle volume has been reported to be an important prognostic factor in patients receiving treatments for other types of

cancers.⁴³ In the present study, a fair percentage of our patients (35.3%) had MVL and a relative decline in muscle volume at 4 and 12 weeks after starting LEN was observed in patients who had data of CT imaging findings available, similar to our past study of patients treated with SOR.⁴¹ It will be important to analyze the relationships among therapeutic response, OSR, and muscle volume in patients undergoing LEN therapy in a future study. Although some trials of intervention with nutrition and exercise CLD patients have been reported,^{44,45} effective intervention methods have yet to be reported. Establishment of strategies for preventing and improving muscle wasting in CLD patients with and without HCC is needed for improving prognosis.

The present study has some limitations, including its retrospective nature. Additionally, though this was a multicenter study, the number of analyzed patients was not large and the observation period was limited. In a future study, we hope to examine the relationship between prognosis and clinical features including AEs and muscle volume with a larger number of patients receiving LEN therapy.

In summary, regardless of previous TKI treatments, therapeutic response and AE occurrence following introduction of LEN treatments were similar. We consider that LEN might complement the unmet need for TKI therapy for patients with u-HCC.

CONFLICT OF INTEREST

None declared.

ORCID

Atsushi Hiraoka  <https://orcid.org/0000-0003-1989-0480>

Hidenori Toyoda  <https://orcid.org/0000-0002-1652-6168>

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