

Efficacy and Safety of Lenvatinib Therapy for Unresectable Hepatocellular Carcinoma in a Real-World Practice in Korea

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Keywords

Lenvatinib · Hepatocellular carcinoma · Efficacy · Safety · Real-world practice

Abstract

Background: Lenvatinib has been recently approved as a first-line treatment option for patients with unresectable hepatocellular carcinoma (HCC) in Korea. We aimed to study the efficacy and safety of lenvatinib therapy in a real-world practice and to find prognostic factors related to survival and disease progression. **Methods:** A hospital-based retrospective study was conducted on 111 consecutive patients who had unresectable HCC and were treated with lenvatinib at Samsung Medical Center from October 2018 to March 2020. Efficacy was determined using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria in 111 patients who completed 1st tumor assessment. Safety was evaluated in 116 HCC patients including 5 patients who discontinued lenvatinib due to adverse events (AEs) before 1st tumor assessment using Common Terminology Criteria for AEs version 5.0. **Results:** A total of 111 patients with a median age of 59 years were analyzed during a median follow-up duration of 6.2 (4.4–9.0) months. The Kaplan-Meier esti-

mate of overall survival was 10.5 months, and the median progression-free survival was 6.2 months. Based on mRECIST criteria, the objective response rate was 18.9% and disease control rate was 75.7%. AEs developed in 86/116 (74.1%) patients, and grade ≥ 3 AEs developed in 16/116 (13.8%) patients. Diarrhea, hand-foot skin rash, abdominal pain, hypertension, and anorexia were identified as the AEs with the highest frequencies of any grade. REFLECT eligibility criteria including tumor extent $\geq 50\%$ liver occupation or inadequate bone marrow function and occurrence of anorexia were prognostic factors for survival, and occurrence of diarrhea was a favorable factor for disease progression. **Conclusion:** Lenvatinib therapy showed a favorable efficacy and safety in a real-world practice. The REFLECT eligibility criteria and specific AEs could be one of the prognostic markers.

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related death worldwide [1]. Despite the advancements in imaging tests and therapeutic techniques during the last

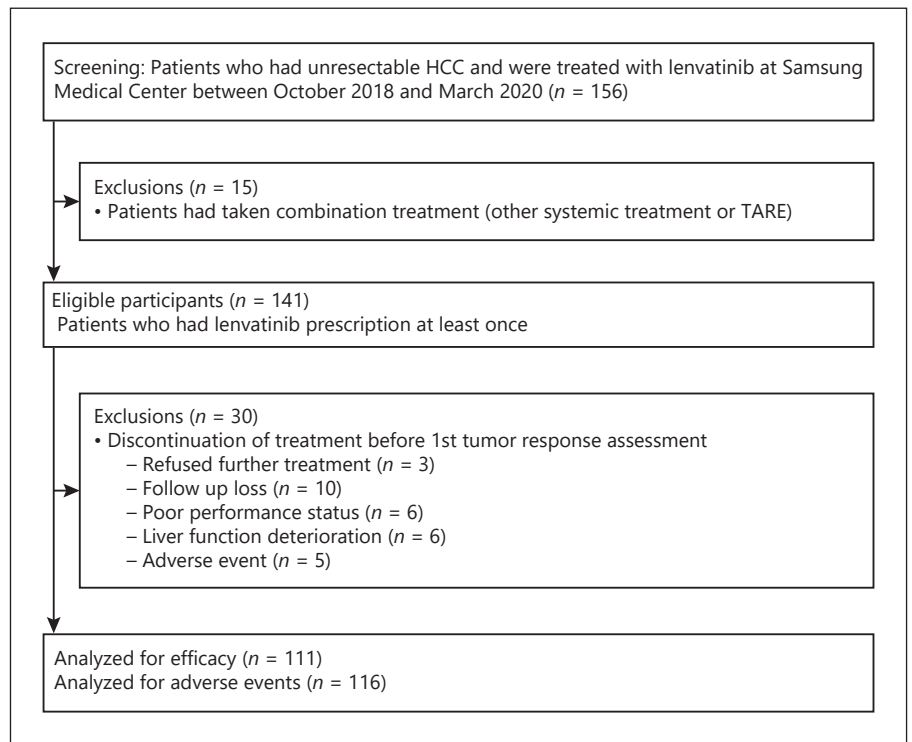


Fig. 1. Patient flow. HCC, hepatocellular carcinoma.

decade, the prognosis of advanced HCC is still poor that 5-year survival rates are just 18% [2]. For patients with advanced stage and intermediate stage unsuitable for locoregional treatment, systemic treatment is the only therapeutic option [3].

Sorafenib, an oral multityrosine kinase inhibitor (TKI), has been the first-line treatment for advanced HCC since 2007, when the SHARP trial demonstrated that sorafenib improved median overall survival (OS) compared to placebo in patients with advanced HCC (10.7 vs. 7.9 months, $p < 0.001$) [4]. For 10 years thereafter, numerous studies assessing new targeted agents as monotherapy including brivanib, sunitinib, and linifanib [5–7] or in combination with sorafenib including doxorubicin [8] and erlotinib [9] failed to demonstrate superiority or noninferiority compared to sorafenib in the first-line setting [10].

In 2018, lenvatinib, an oral TKI that inhibits VEGF receptors 1–3, FGF receptors 1–4, PDGF receptor α , RET, and KIT [11], has been emerging as the first drug to show noninferiority compared to sorafenib in the first-line treatment for unresectable HCC patients [12]. The REFLECT trial, an open-label, phase 3, multicenter trial demonstrated that lenvatinib showed not only comparable OS with sorafenib (13.6 vs. 12.3 months) but also significant improvement in treatment response (overall re-

sponse rate 40.6 vs. 12.4%) and median progression-free survival (PFS) duration (7.4 vs. 3.7 months) [12].

Accordingly, lenvatinib has been recently approved as the first-line treatment option for patients with unresectable HCC in Korea. We aimed to study the efficacy and safety of lenvatinib therapy in a real-world practice and to find prognostic factors related to survival and disease progression.

Methods

Study Design and Patients

This was a hospital-based retrospective cohort study. Patients who had unresectable HCC with diagnoses confirmed histologically or clinically in accordance with the regional HCC guideline [13, 14] and were treated with lenvatinib at least once at Samsung Medical Center from October 1, 2018, to March 31, 2020, were screened for potential inclusion in the study. Among the 156 eligible patients, patients were excluded if they had taken concomitant treatment with other systemic treatment or locoregional therapy ($n = 15$), discontinuation of treatment before 1st tumor response assessment due to refusal of further chemotherapy ($n = 3$), follow-up loss ($n = 10$), poor performance status ($n = 6$), liver function deterioration ($n = 6$), or adverse events (AEs) ($n = 5$). A total of 111 consecutive patients with unresectable HCC were analyzed for treatment efficacy. Safety was evaluated in 116 HCC patients including 5 patients who stopped lenvatinib due to AEs before the 1st tumor assessment (Fig. 1).

Data Collection and Definition of Variables

We collected data on clinical characteristics (age, gender, etiology, performance status, baseline hypertension, or diabetes mellitus), laboratory findings (blood cell count, liver function test, tumor markers including alpha-fetoprotein, and protein induced by vitamin K absence or antagonist-II), and radiological findings (the number and size of intrahepatic lesions, macrovascular invasion, and extrahepatic lesions). We also collected data on stage of HCC (Barcelona Clinic Liver Cancer [BCLC] stage [15] and modified Union for International Cancer Control [mUICC] stage [13]) at the introduction time of lenvatinib and previous treatment including resection, transarterial chemoembolization, transarterial radioembolization, radiation therapy, and systemic treatment. Further information for systemic treatment including TKIs (sorafenib and regorafenib) or immunotherapy (pembrolizumab, nivolumab, atezolizumab or durvalumab) were collected. In addition, we collected information for liver function at baseline including Child-Pugh classification and modified ALBI (mALBI) grade. mALBI grade was calculated based on serum albumin and total bilirubin values using the following formula: [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 4 grades: ≤ -2.6 = grade 1; > -2.60 to ≤ -2.27 = grade 2a; > -2.27 to ≤ -1.39 = grade 2b; > -1.39 = grade 3 [16]. Lastly, we collected information for dose of lenvatinib during study period. Relative dose intensity for initial 8 weeks of therapy (8W-RDI) was calculated as the actual cumulative dose within the initial 8 weeks of starting lenvatinib treatment divided by the recommended dose [17]. Patients were scheduled to visit at weeks 6–12 for assessment of treatment response and safety using contrast-enhanced dynamic computed tomography (CT) or magnetic resonance imaging (MRI), laboratory findings including tumor markers, and physical findings.

Treatment Regimens

Lenvatinib was administered orally for patients with unresectable HCC. The lenvatinib dose depended on the patients' weight: those who weighed <60 kg were administered 8 mg of lenvatinib daily, while those who weighed ≥ 60 kg were initially administered 12 mg of lenvatinib daily. Initial dose reduction was made from 12 to 8 mg in patients with poor oral intake, poor hepatic reserve function, or suspicious infection by clinician's own decision. During the study period, dose reduction or treatment interruption was also made in patients who developed AEs of at least grade 2 or AEs considered uncontrollable despite symptomatic management. Lenvatinib was discontinued when any unacceptable or serious AEs or clinical tumor progression was observed.

Assessment of Treatment Response

Initial treatment response was evaluated by contrast-enhanced dynamic CT or MRI at baseline and at 6–12 weeks after treatment initiation. Initial treatment response was assessed according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [18]. Thereafter, radiological evaluation using CT or MRI was carried out every 1–3 months among the patients who did not show disease progression. We also assessed best overall response using mRECIST. Best overall response was defined as the best response recorded from the start of lenvatinib treatment until disease progression. Objective response rate (ORR) was defined as complete response (CR) and partial response (PR), and disease control rate (DCR) was defined as CR, PR, and stable disease (SD).

The efficacy of lenvatinib was further evaluated among patients who did or did not fulfill the REFLECT eligibility criteria (i.e., tumor extent $<50\%$ liver occupation, no obvious invasion of the main portal vein or bile duct, no history of previous systemic treatment, adequate liver/bone marrow function, or no history of liver transplantation at the introduction time of lenvatinib). Definitions for adequate liver or bone marrow function were based on the REFLECT eligibility criteria.

Safety Assessment

Safety assessment included recording of performance status by the Eastern Cooperative Oncology Group (ECOG), vital signs, laboratory testing, urinalysis, and physical findings. Drug-related AEs were graded according to the Common Terminology Criteria for Adverse Events version 5.0. AEs were evaluated in 116 patients including 5 patients who discontinued lenvatinib due to AEs. For safety assessment, patients were evaluated at week 2 of lenvatinib therapy using laboratory tests and physical findings. Thereafter, safety assessment was performed with treatment response assessment every 1–3 months. As in the treatment response analysis, AEs were further evaluated stratified to whether patients fulfilled the REFLECT eligibility criteria or not.

Factors Associated with Overall Survival and Disease Progression

We evaluated whether survival and disease progression were different among patients who did or did not fulfill the REFLECT eligibility criteria. Subgroup analysis was conducted based on each detailed criteria of REFLECT eligibility criteria. Furthermore, we evaluated the association between AEs and prognosis of HCC in patients treated with lenvatinib therapy. Likewise, subgroup analysis was conducted based on each AE. However, abdominal pain was not included in this analysis since it was difficult to distinguish cancer pain.

Statistical Analysis

Continuous variables were expressed as the median with interquartile range (IQR). The categorical variables were expressed as counts with percentages. The continuous variables were compared using Mann-Whitney U tests and the categorical variables using Fisher's exact test. The Kaplan-Meier method was used to estimate OS and PFS. To identify the factors associated with OS and disease progression, multivariable analysis was performed using the Cox proportional hazard model for variables with p values of <0.10 in the univariable analysis. Components of REFLECT eligibility criteria and individual AEs were analyzed, respectively, to identify prognostic factors. Statistical analyses were performed using SPSS statistics 25.0 (IBM Corp., Armonk, NY, USA), and $p < 0.05$ was considered statistically significant.

Results

Patient Characteristics

A total of 111 patients were analyzed for efficacy after exclusion, and their characteristics are shown in Table 1. The median patient age was 59 years (range, 49–67 years), and 96 (86.5%) patients were male. Most patients (94.6%)

Table 1. Baseline characteristics of the patients

	Entire cohort (N = 111)	Fulfill REFLECT criteria (n = 48)	Did not fulfill REFLECT criteria (n = 63)	p value
Age, years	59 (49–67)	57 (49–65)	60 (48–68)	0.48
Male	96 (86.5)	41 (85.4)	55 (87.3)	0.79
ECOG PS ≥ 1	24 (21.6)	10 (20.8)	14 (22.2)	1.00
Previous history of hypertension	37 (33.3)	17 (35.4)	20 (31.7)	0.69
Previous history of diabetes	21 (18.9)	13 (27.1)	8 (12.7)	0.09
Etiology (VH vs. non-VH)	85:26	34:14	51:12	0.26
BCLC stage C	105 (94.6)	45 (93.8)	60 (95.2)	1.00
mUICC stage (III:IV-A:IV-B)	7:13:91	3:6:39	4:7:52	0.98
Intrahepatic lesions (0:1:2:3)	19:26:11:55	6:16:5:21	13:10:6:34	0.16
Macrovascular invasion	55 (49.5)	20 (41.7)	35 (55.6)	0.18
Extrahepatic lesion	91 (82.0)	39 (81.3)	52 (82.5)	1.00
Previous systemic treatment	15 (13.5)	0 (0.00)	15 (23.8)	<0.001
Previous TKIs	12	0	12	
Immune checkpoint inhibitors	12	0	12	
Both	9	0	9	
Initial dose reduction	14 (12.6)	4 (8.3)	10 (15.9)	0.27
Dose modification	46 (41.4)	19 (39.6)	27 (42.9)	0.85
8W-RDI, %, median (min, max)	100 (41.1–100)	100 (44–100)	100 (41.1–100)	0.54
ANC × 10 ³ /μL	3.6 (2.5–4.5)	3.2 (2.5–4.6)	3.7 (2.4–4.5)	0.93
Hemoglobin, g/dL	13.6 (12.3–15.0)	13.8 (12.5–15.5)	13.5 (12.3–14.6)	0.24
Platelet count × 10 ³ /μL	150 (111–204)	155 (115–206)	143 (97–204)	0.46
Total bilirubin, mg/dL	0.7 (0.5–1.1)	0.6 (0.5–0.9)	0.9 (0.5–1.3)	0.02
AST, U/L	50.0 (33.0–95.0)	45.5 (34.0–59.5)	53.0 (33.0–116.0)	0.07
ALT, U/L	33.0 (22.0–60.0)	32.5 (22.0–52.3)	33.0 (23.0–75.0)	0.22
ALP, U/L	129 (102–171)	133 (106–158)	127 (96–201)	0.82
PT, INR	1.04 (0.99–1.12)	1.03 (0.97–1.08)	1.06 (1.01–1.17)	0.02
Albumin, g/dL	4.1 (3.7–4.3)	4.1 (3.9–4.5)	4.0 (3.6–4.3)	0.03
Child-Pugh score (5:6:7:8)	84:23:3:1	41:7:0:0	43:16:3:1	0.13
Modified ALBI (grade 1:2a:2b:3)	20:32:48:11	11:18:17:2	9:14:31:9	0.06
AFP, ng/mL	386 (11–5,309)	163 (12–1,392)	548 (9–13,220)	0.40
PIVKA-II, mAU/mL	562 (41–13,421)	200 (91–3,400)	865 (46–42,143)	0.08
Median follow-up duration	6.2 (4.4–9.0)	7.2 (4.5–9.6)	5.7 (4.2–8.9)	0.01

Data are presented as median (range) or *n* (%). ECOG PS, Eastern Cooperative Oncology Group performance status; VH, viral hepatitis; BCLC, Barcelona Clinic Liver Cancer; mUICC, modified Union for International Cancer Control; TKIs, tyrosine kinase inhibitors; 8W-RDI, relative dose intensity of lenvatinib within 8 weeks; ANC, absolute neutrophil count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time; INR, international normalized ratio; AFP, alpha-fetoprotein.

were diagnosed with BCLC stage C, and 91 (82.0%) patients had extrahepatic lesions. The median follow-up duration was 6.2 months (range 4.4–9.9 months). Fifteen (13.5%) patients had experienced previous systemic treatment including other oral TKIs, immunotherapy, or both (sorafenib [*n* = 12], regorafenib [*n* = 4], pembrolizumab [*n* = 2], nivolumab [*n* = 3], durvalumab [*n* = 5], and atezolizumab [*n* = 2]). In 14 (12.6%) patients with poor oral intake, poor liver function (Child-Pugh score B, total bilirubin >3 mg/dL, and aspartate/alanine transaminase >5

× upper limit of normal range), or fever/high C-reactive protein, initial dose modification from 12 to 8 mg of lenvatinib was performed by clinician's own decision. Sixty-three (56.8%) patients did not fulfill the REFLECT eligibility criteria due to tumor extent ≥50% liver occupation, main portal vein/bile duct invasion, previous systemic treatment, inadequate liver/bone marrow function, or history of liver transplantation (online suppl. Fig. 1; see www.karger.com/doi/10.1159/000512239) for all online suppl. material. There was no significant difference in

Table 2. Clinical response of lenvatinib according to REFLECT eligibility criteria at initial tumor assessment

Response	Overall cohort	Fulfilled REFLECT eligibility criteria	Did not fulfill REFLECT eligibility criteria	<i>p</i> value
Complete response, <i>n</i> (%)	1 (0.9)	0 (0.0)	1 (1.6)	
Partial response, <i>n</i> (%)	20 (18.0)	10 (20.8)	10 (15.9)	
Stable disease, <i>n</i> (%)	63 (56.8)	31 (64.6)	32 (50.8)	
Progressive disease, <i>n</i> (%)	27 (24.3)	7 (14.6)	20 (31.7)	
Objective response rate	18.9%	20.8%	17.5%	0.81
Disease control rate	75.7%	85.4%	68.3%	0.045

Data are presented as *n* (%).

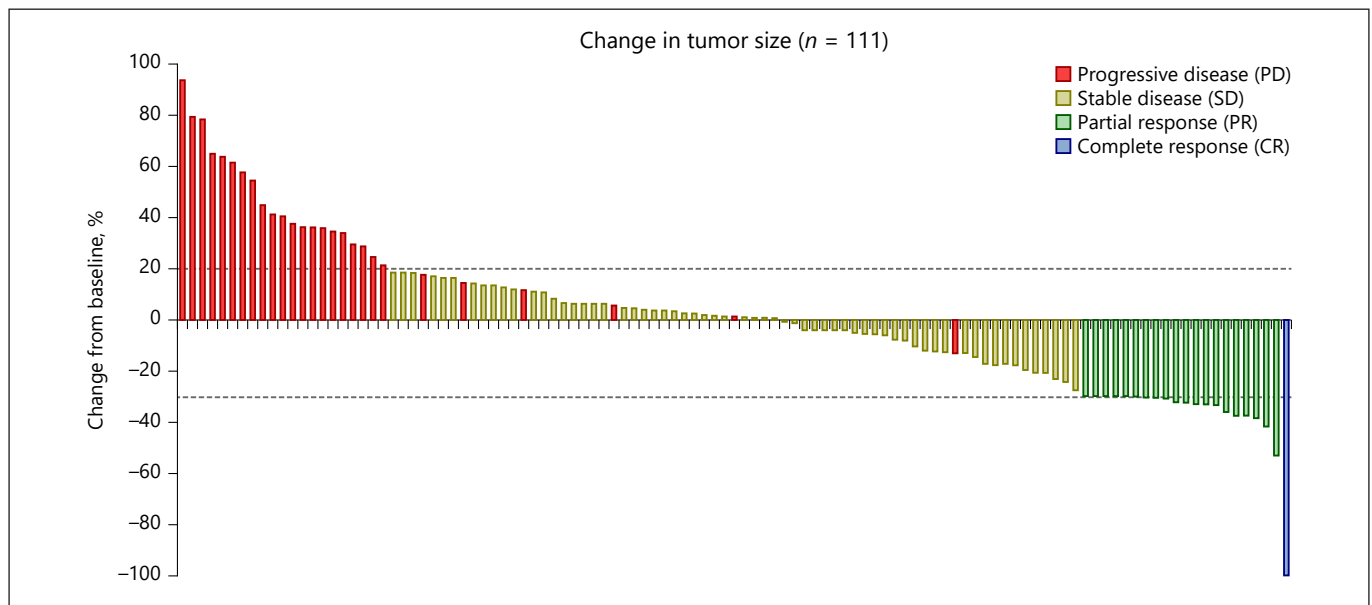


Fig. 2. Tumor reduction rate in the target lesion by mRECIST at the 1st tumor assessment in 111 patients. CR/PR was shown in 21 (18.9%) patients, SD in 63 (56.8%), and PD in 27 (24.3%) patients, respectively. mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

baseline characteristics among patients who did or did not fulfill the REFLECT eligibility criteria except hepatic reserve function. Patients who did not fulfill the REFLECT eligibility criteria showed significantly higher portion of Child-Pugh score ≥ 6 (14.6 vs. 31.7%) and mALBI grade $\geq 2b$ (39.5 vs. 63.5%).

Treatment Response

The first evaluation of the therapeutic efficacy of lenvatinib was performed at weeks 6–12 of lenvatinib. Based on mRECIST criteria, CR/PR was shown in 21 (18.9%)

patients, SD in 63 (56.8%), and PD in 27 (24.3%) patients (ORR 18.9%; DCR 75.7%) (Fig. 2). Initial treatment response was the best overall treatment response during the study period. When comparing treatment response by mRECIST according to whether patients fulfilled the REFLECT eligibility criteria or not, there was no significant difference in ORR (20.8 vs. 17.5%, *p* value = 0.81) but there was significant difference in DCR (85.4 vs. 68.3%, *p* value = 0.045) (Table 2). The Kaplan-Meier estimate of median OS was 10.5 months, and the median PFS was 6.2 months.

Table 3. Adverse events ($N = 116$)

	Entire cohort ($N = 116$)			Fulfilled REFLECT eligibility criteria ($n = 52$)			Did not fulfill REFLECT eligibility criteria ($n = 64$)			p value
	grade 1/2	grade 3/4	any grade	grade 1/2	grade 3/4	any grade	grade 1/2	grade 3/4	any grade	
Hand-foot skin reaction	27	3	30 (14.0)	14	1	15 (13.8)	13	2	15 (14.3)	0.53
Diarrhea	24	2	26 (12.1)	12	0	12 (11.0)	12	2	14 (13.3)	1.00
Abdominal pain	23	3	26 (12.1)	11	0	11 (10.1)	12	3	15 (14.3)	0.83
Hypertension	21	2	23 (10.7)	11	1	12 (11.0)	10	1	11 (10.5)	0.49
Anorexia	16	0	16 (7.5)	5	0	5 (4.6)	11	0	11 (10.5)	0.29
Constipation	12	0	12 (5.6)	7	0	7 (6.4)	5	0	5 (4.8)	0.37
Nausea/vomiting	11	0	11 (5.1)	4	0	4 (3.7)	7	0	7 (6.7)	0.75
Generalized weakness	10	0	10 (4.7)	6	0	6 (5.5)	4	0	4 (3.8)	0.34
Skin rash	8	1	9 (4.2)	6	1	7 (6.4)	2	0	2 (1.9)	0.08
Oral mucositis	7	0	7 (3.3)	5	0	5 (4.6)	2	0	2 (1.9)	0.24
Dysphonia	7	0	7 (3.3)	3	0	3 (2.8)	4	0	4 (3.8)	1.00
Elevated aspartate/ alanine aminotransferase	3	3	6 (2.8)	1	3	3 (2.8)	3	0	3 (2.9)	1.00
Headache	5	0	5 (2.3)	2	0	2 (1.8)	3	0	3 (2.9)	1.00
Hypothyroidism	5	0	5 (2.3)	2	0	2 (1.8)	3	0	3 (2.9)	1.00
Fever within 2 weeks	5	0	5 (2.3)	2	0	2 (1.8)	3	0	3 (2.9)	1.00
Proteinuria	3	1	4 (1.9)	3	1	4 (3.7)	0	0	0 (0.0)	0.04
Epistaxis	4	0	4 (1.9)	3	0	3 (2.8)	1	0	1 (1.0)	0.32
Myalgia/arthralgia	3	0	3 (1.4)	2	0	2 (1.8)	1	0	1 (1.0)	0.59
Itching	3	0	3 (1.4)	3	0	3 (2.8)	0	0	0 (0.0)	0.09
Posterior reversible encephalopathy syndrome	0	1	1 (0.5)	0	1	1 (0.9)	0	0	0 (0.0)	0.45
Alopecia	1	0	1 (0.5)	0	0	0 (0.0)	1	0	1 (1.0)	1.00
Total events	198 (92.5)	16 (7.5)	214 (100)	102 (94.5)	8 (6.5)	109 (100)	97 (93.3)	8 (6.7)	105 (100)	
Patients developing adverse events	70 (60.3)	16 (13.8)	86 (74.1)	32 (61.5)	8 (15.4)	40 (76.9)	38 (59.3)	8 (12.5)	46 (71.9)	0.67

Data are presented as n (%).

Safety Assessment

A total of 214 AEs occurred in 86 of 116 (74.1%) patients, and \geq grade 3 AEs developed in 16 of 116 (13.8%) patients (Table 3). Hand-foot skin reaction (HFSR), diarrhea, abdominal pain, hypertension, and anorexia were identified as the AEs with the highest frequencies of any grade. HFSR, diarrhea, abdominal pain, and elevated aspartate/alanine aminotransferase were identified as the AEs with the highest frequencies of grade 3 or 4. Most AEs could be controlled by carrying out appropriate dose reduction, interruption, and symptomatic treatment. During the study period, dose reduction or interruption was performed in 35 (31.5%) patients and 11 (9.9%) patients discontinued lenvatinib due to cost ($n = 1$), deterioration of performance status ($n = 2$), recurrent hepatic encephalopathy ($n = 4$), intolerable abdominal pain ($n = 1$), and infection ($n = 3$). There were 5 (4.3%) patients who discontinued lenvatinib therapy before the first treatment response evaluation due to AEs of skin rash

(grade 3), posterior reversible encephalopathy syndrome (grade 4), nausea/diarrhea/abdominal pain/hyperbilirubinemia (all grade 2), aspartate/alanine transaminase elevation (grade 3), and anorexia (grade 2) with aspartate/alanine transaminase elevation (grade 3), respectively. Frequency of AEs was not different among patients who did or did not fulfill the REFLECT eligibility criteria (Table 3).

Factors Associated with Overall Survival and Disease Progression

When stratified according to whether patients fulfilled the REFLECT eligibility criteria or not, the Kaplan-Meier estimate of median OS was significantly different: 13.9 months (95% confidence interval [CI]: 8.1–19.7) versus 8.7 months (95% CI: 7.6–9.8), $p_{\log \text{rank}} = 0.006$ (Fig. 3a). In univariable analysis, REFLECT criteria (i.e., tumor extent $\geq 50\%$ of liver occupation, bile duct invasion, and inadequate bone marrow function), mALBI grade $\geq 2b$, and an-

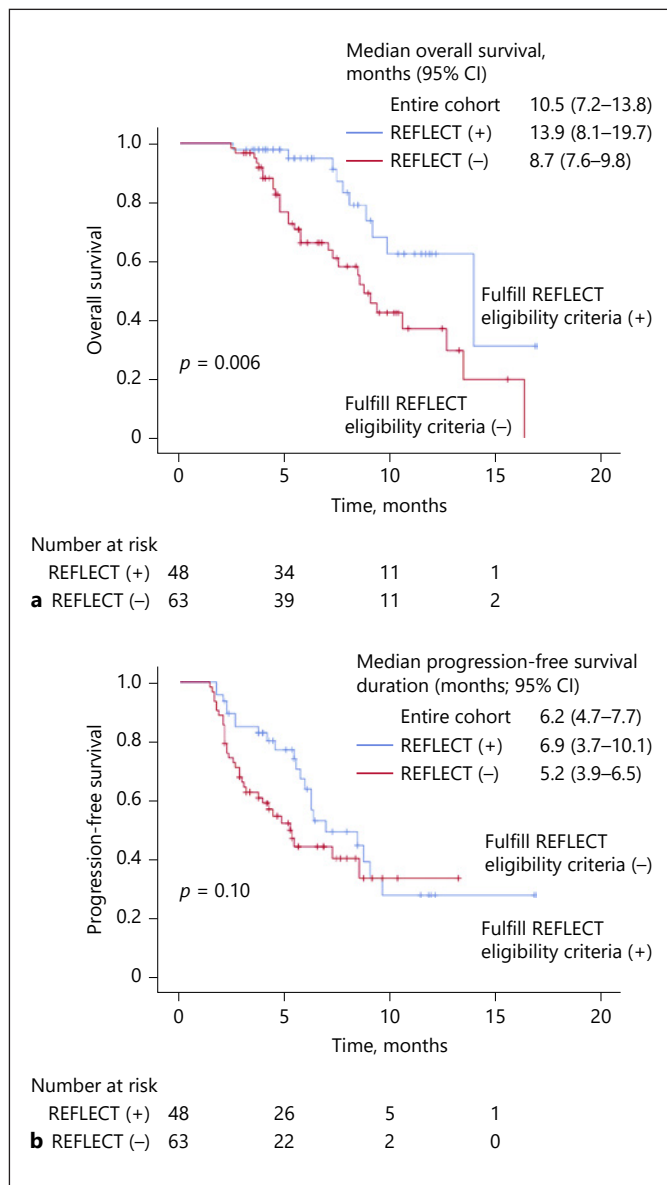


Fig. 3. Kaplan-Meier estimates of overall survival (a) and progression-free survival (b) according to whether patients fulfill the REFLECT eligibility criteria or not.

orexia of AEs were significantly associated with OS. In multivariable analysis, tumor extent $\geq 50\%$ of liver occupation (adjusted hazard ratio [HR] = 4.37; 95% CI: 2.00–9.58) and inadequate bone marrow function (HR = 3.77; 95% CI: 1.47–9.68) among REFLECT eligibility criteria and anorexia (HR = 2.15; 95% CI: 1.01–4.58) among AEs were found as poor prognostic factors for OS (Table 4).

However, whether patients fulfill the REFLECT eligibility criteria or not was not a significant prognostic fac-

tor in PFS (6.9 months [95% CI: 3.7–10.1] vs. 5.2 months [95% CI: 3.9–6.5], $p_{\log \text{rank}} = 0.10$) (Fig. 3b). Tumor extent $\geq 50\%$ of liver occupation was the only REFLECT eligibility criteria associated with poor PFS in univariable analysis. Meanwhile, specific AEs were significantly associated with PFS; occurrence of HFSR or diarrhea was associated with favorable PFS, and anorexia was associated with poor PFS. In multivariable analysis, diarrhea was found as the only favorable prognostic factor for disease progression during lenvatinib therapy (HR = 0.37; 95% CI: 0.17–0.84) (Table 5).

Discussion

In this study, lenvatinib showed a favorable efficacy and safety for patients with unresectable HCC in a real-world setting, though more than half of the patients ($n = 63$, 57.2%) did not fulfill the REFLECT eligibility criteria. The ORR and DCR at initial treatment response at weeks 6–12 after starting lenvatinib was 18.9 and 75.7%, which is consistent with the REFLECT trial (ORR: 24% and DCR: 75.5% by investigator review according to mRECIST) [12].

However, the current study found that patients who fulfilled the REFLECT eligibility criteria showed better DCR and OS than those of patients who did not fulfill the REFLECT eligibility criteria (DCR: 85.4 vs. 68.3%, p value 0.045, median OS duration: 13.9 months [8.1–19.7] vs. 8.7 months [7.6–9.8]), which confronts the result from the recent Japanese study of 41 patients with unresectable HCC [19]. This is due to the difference in detail components of patients who did not fulfill the REFLECT eligibility criteria. In the previous study, patients did not fulfill the REFLECT eligibility criteria mainly due to history of previous systemic treatment (16/23, 69.6%) and all of them fulfill the REFLECT eligibility criteria of tumor extent. In contrast, about one-third (20/63, 31.7%) had tumor extent $\geq 50\%$ liver occupation in the current study. Among detail components of REFLECT eligibility criteria, tumor extent $\geq 50\%$ liver occupation and inadequate bone marrow function were important prognostic factors for OS, but history of previous systemic treatment was not associated with OS or PFS in this study. There was no significant difference between patients who fulfilled the REFLECT eligibility criteria ($n = 48$) and patients who did not fulfill the REFLECT eligibility criteria only due to history of previous systemic treatment ($n = 11$) in OS and PFS (online suppl. Fig. 2) though the analysis is limited due to the small number of patients.

Table 4. Multivariable Cox regression analysis for overall survival

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Age ≥59, median	1.43 (0.75–2.72)	0.28		
Male	1.17 (0.45–3.01)	0.75		
ECOG ≥1	1.55 (0.78–3.12)	0.22		
Etiology (VH vs. non-VH)	0.80 (0.40–1.62)	0.54		
mALBI ≥2b	2.02 (1.05–3.87)	0.03	1.31 (0.63–2.74)	0.48
mUICC (III, IV-A vs. IV-B)	0.96 (0.40–2.29)	0.92		
Intrahepatic lesion	2.02 (0.78–5.18)	0.15		
Extrahepatic involvement	0.98 (0.41–2.35)	0.96		
≥50% liver volume	3.11 (1.52–6.33)	0.002	4.37 (2.00–9.58)	<0.001
Main portal vein involvement	0.84 (0.37–1.93)	0.68		
Bile duct involvement	6.09 (1.76–21.0)	0.004	3.67 (0.96–14.1)	0.06
Previous systemic treatment	0.79 (0.33–1.89)	0.59		
Inadequate liver function	2.31 (0.80–6.68)	0.12		
Inadequate bone marrow function	3.22 (1.43–7.25)	0.005	3.77 (1.47–9.68)	0.006
History of LT	0.95 (0.23–3.94)	0.94		
8W-RDI <100%, median	1.53 (0.71–3.27)	0.28		
AFP ≥386, median	1.58 (0.84–2.98)	0.16		
PIVKA-II ≥562, median	1.46 (0.78–2.74)	0.24		
HFSR	0.75 (0.36–1.59)	0.45		
Diarrhea	0.57 (0.25–1.30)	0.18		
Hypertension	0.92 (0.38–2.22)	0.86		
Anorexia	2.55 (1.27–5.13)	0.009	2.15 (1.01–4.58)	0.05
History of hypertension	1.81 (0.94–3.45)	0.08	1.78 (0.87–3.64)	0.11
History of diabetes	1.43 (0.68–3.01)	0.35		

HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; VH, viral hepatitis; mALBI, modified ALBI; LT, liver transplantation; 8W-RDI, relative dose intensity of lenvatinib within 8 weeks; AFP, alpha-fetoprotein; HFSR, hand-foot skin reaction.

Tumor burden and hepatic reserve function were the 2 most important factors in the prognosis of HCC [20, 21]. A previous multicenter study of 152 patients with unresectable HCC in Japan found that mALBI ≥2b was the only prognostic factor for survival [22]. mALBI grade was also one of the prognostic factors in the univariable analysis in the current study but not in the multivariable analysis. This different result may be attributed to the difference in included patient characteristics. Patients with higher proportion of far advanced stage of HCC were included in the current study such as mUICC stage IV (93.7 vs. 51.3%) and extrahepatic metastases (82.0 vs. 50%). Tumor burden could be more important factor than hepatic reserve function in patients with far advanced HCC.

However, we found that bone marrow function is one of the important prognostic factors for survival. Of 14 patients with inadequate bone marrow function, 1 patient did not meet hemoglobin <8.5 g/dL, 2 patients did not meet ANC <1,500/μL, and rest of them did not meet

platelet <75,000/μL. This finding implicated that thrombocytopenia, which is the hallmark of advanced liver cirrhosis and portal hypertension [23], was associated with poor survival for advanced HCC. It is consistent with the result of recent meta-analysis that thrombocytopenia seems to be associated with poor OS and recurrence-free survival [24].

In the current study, 74.1% patients experienced at least one AE. The most common AEs of any grade were similar to those in the REFLECT trial, which included HFSR, diarrhea, and hypertension. However, proteinuria was developed in only 4 (1.9%) patients in this study compared to 117/476 (25%) patients in the REFLECT trial. Grade ≥3 AEs occurred in 16 of 116 (13.8%) patients, which has much lower frequency than those in the previous studies [12, 25]. In particular, there was only 2 (1.7%) patients who need ≥2 uncontrolled hypertension or SBP >160 during study period compared to 15–25% of patients developed hypertension ≥grade 3 in previous stud-

Table 5. Multivariable Cox regression analysis for progression-free survival

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Age ≥59, median	1.07 (0.64–1.83)	0.78		
Male	1.20 (0.54–2.66)	0.66		
ECOG ≥1	1.75 (0.96–3.20)	0.07	1.81 (0.96–3.40)	0.07
Etiology (VH vs. non-VH)	1.53 (0.79–2.97)	0.21		
mALBI ≥2b	1.06 (0.62–1.81)	0.83		
mUICC (III, IV-A vs. IV-B)	1.50 (0.64–3.50)	0.35		
Intrahepatic lesion	1.31 (0.64–2.68)	0.47		
Extrahepatic involvement	1.59 (0.68–3.72)	0.29		
≥50% liver volume	2.01 (1.02–3.96)	0.04	1.46 (0.72–2.94)	0.29
Main portal vein involvement	0.85 (0.4–1.80)	0.67		
Bile duct involvement	1.53 (0.37–6.38)	0.56		
Previous systemic treatment	1.46 (0.73–2.93)	0.28		
Inadequate liver function	1.36 (0.49–3.877)	0.56		
Inadequate bone marrow function	1.40 (0.63–3.13)	0.41		
History of liver transplantation	1.44 (0.45–4.65)	0.54		
8W-RDI <100%, median	1.00 (0.99–1.02)	0.98		
AFP > 386, median	1.16 (0.69–1.98)	0.57		
PIVKA-II > 562, median	1.16 (0.68–1.97)	0.59		
HFSR	0.38 (0.19–078)	0.008	0.51 (0.24–1.08)	0.08
Diarrhea	0.30 (0.13–0.66)	0.003	0.37 (0.17–0.84)	0.02
Hypertension	0.64 (0.30–1.34)	0.24		
Anorexia	1.83 (0.96–3.47)	0.07	1.51 (0.78–2.94)	0.22
History of hypertension	1.36 (0.78–2.37)	0.27		
History of diabetes	1.51 (0.81–2.82)	0.20		

HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; VH, viral hepatitis; mALBI, modified ALBI; 8W-RDI; relative dose intensity of lenvatinib within 8 weeks; AFP, alpha-fetoprotein; HFSR, hand-foot skin reaction.

ies [12, 25, 26]. Hence, compliance to lenvatinib therapy in these study patients was good, reflecting a median 8W-RDI of 100%. There was no significant difference in AE occurrence rates and 8W-RDI among patients who did or did not fulfill the REFLECT eligibility criteria (Tables 1, 3).

In addition, we investigated survival or disease progression according to each AE. The presence of HFSR has been regarded as a favorable factor of OS in patients treated with sorafenib [27] and regorafenib [28]. There were several studies that found specific AEs were associated with favorable outcome of lenvatinib therapy reflecting longer OS or time to progression (TTP) [22, 26, 29]; however, it is still inconclusive. In the current study, we found anorexia was the only factor associated with poor OS (HR = 2.15, 95% CI: 1.01, 4.58) after adjustment for factors related to tumor burden and hepatic reserve function. Moreover, we found that diarrhea and HFSR have

the potential to predict longer TTP during lenvatinib therapy. Diarrhea was the only favorable prognostic factor for disease progression in multivariable analysis (HR = 0.37; 95% CI: 0.17–0.84, *p* value = 0.02), while HFSR was only marginally associated (HR = 0.51; 95% CI: 0.24–1.08, *p* value = 0.08).

Of note, there were 23 (20.7%) patients who received palliative radiation therapy within 1 month or during lenvatinib therapy. Palliative radiation therapy was performed to portal vein/hepatic vein tumor thrombus (*n* = 4), bone metastasis (*n* = 8), lymph node (*n* = 3), peritoneal seeding nodule (*n* = 3), or main liver lesion (*n* = 5). There was no dose modification of lenvatinib for considering additive AEs due to radiation therapy. However, radiation therapy within 1 month or during lenvatinib therapy was not significantly aggravated developing AEs of any grade. Efficacy evaluated by initial treatment response at weeks 6–12 during lenvatinib was higher in pa-

tients who received concurrent radiation therapy; however, ORR (18.2%) and DCR (73.9%) was still favorable after excluding patients who received radiation therapy (online suppl. Table 1). Receiving radiation therapy within 1 month or during lenvatinib therapy was not significantly associated with OS or disease progression (data not shown).

The strength of our study is a relatively homogenous cohort, in which the patients included in this study were mostly consisted of BCLC stage C/mUICC stage IV HCC with extrahepatic metastases. However, there are several limitations. First of all, this study was a retrospective study from a single tertiary center of a single ethnicity. Moreover, the number of cases and observation period were limited. Nevertheless, we found that tumor extent $\geq 50\%$ liver volume and anorexia were poor prognostic factors for survival in patients with far advanced HCC and diarrhea among AEs was favorable prognostic factors for disease progression during lenvatinib therapy. This finding would be helpful to predict outcome of patients who were treated with lenvatinib therapy in the real-world clinical practice.

In conclusion, lenvatinib therapy showed a favorable efficacy and safety in a real-world practice, even though patients who did not meet the REFLECT eligibility criteria were included in this study. In addition, whether patients fulfilled the REFLECT eligibility criteria or not and the presence of specific AEs (anorexia and diarrhea) could be the prognostic factors associated with survival and disease progression during lenvatinib therapy.

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Statement of Ethics

This study was performed in accordance with the Declaration of Helsinki, and it has been approved by the Institutional Review Board at the Samsung Medical Center (IRB No. 2020-03-119-001). As the study used only deidentified data routinely collected during hospital visits, the requirement of obtaining informed consent from the patients was waived.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (NRF-2016R1C1B2015463 and NRF-2019R1C1C1007729).

Author Contributions

M.J.G. and W.K.: study design, statistical analysis, and drafting of the manuscript. J.H.O., Y.P., and J.K.: data interpretation and critical revision of the manuscript. D.H.S., G.Y.G., and M.S.C.: study design, study supervision, and critical revision of the manuscript. Y.H.P.: study design, drafting of the manuscript, and study supervision. J.H.L.: study supervision, statistical analysis, and data interpretation. K.C.K.: study design, study supervision, and data interpretation. S.W.P.: study supervision, data interpretation, and critical revision of the manuscript. All authors approved the final submission.

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