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ORIGINAL ARTICLE

The efficacy and safety of lenvatinib for advanced hepatocellular carcinoma in a real-world setting

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Abstract

Background/purpose Lenvatinib (an inhibitor of vascular endothelial growth factor (GF) receptors 1–3, fibroblast GF receptors 1–4, platelet-derived GF receptor α, rearranged during transfection, and stem cell factor receptor) was non-inferior to sorafenib in a phase 3 (REFLECT) trial of advanced hepatocellular carcinoma. This study examined the efficacy and safety of lenvatinib in a real-world setting.

Methods This was a retrospective, multicenter, observational study. Inclusion and exclusion criteria were based on the phase 3 trial, and participants were observed for at least 12 weeks. Therapeutic effect was determined using the modified Response Evaluation Criteria In Solid Tumors (m-RECIST) at the 8th week. Patients received oral lenvatinib 12 mg/day (body weight > 60 kg) or 8 mg/day (body weight < 60 kg). Dose interruptions followed by reductions for lenvatinib-related toxicities were permitted. Grades of adverse events (AEs) complied with the Common Terminology Criteria for Adverse Events version 4.0.

Results All 16 patients included in this study had prior treatment history, and a median 3.9 years had passed since the first treatment. Fatigue, hypertension, and proteinuria were the most frequent AEs, and were higher than Grade 2. AEs could be controlled by appropriate dose reduction, interruption, and symptomatic treatment according to the protocol. In the m-RECIST evaluation at the 8th week, 0, 6, 8, and 1 patients had achieved complete response, partial response, stable disease, and progressive disease, respectively. The objective response rate was 40%.

Conclusion Lenvatinib treatment could be accomplished with safety and good response in a real-world setting.

Keywords Lenvatinib · Hepatocellular carcinoma · Clinical practice · Efficacy

Introduction

Hepatocellular carcinoma (HCC) is the most common malignant hepatobiliary disease, the second most common cause of death from cancer worldwide, and estimated to be responsible for nearly 745,000 deaths in 2012 [1]. Despite screening systems, many cases are diagnosed at advanced stages [2, 3]. Furthermore, the natural history of HCC is characterized mostly by intrahepatic spread with metachronous and multicentric carcinogenesis [4]. These events indicate a poor prognosis. For advanced HCC stages, the recommended treatment strategy is sorafenib, an oral multikinase inhibitor [5]. Sorafenib is the only systemic therapy proven to extend overall survival when used as a first-line treatment in Asian cohorts [6, 7].

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In the past 10 years, no approved first-line systemic treatments were available for advanced unresectable HCC other than sorafenib [8–11]. In 2018, lenvatinib (an inhibitor of vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, rearranged during transfection, and stem cell factor receptor) showed non-inferiority in terms of overall survival, as well as statistically significant improvement in progression-free survival, time to progression, and objective response rate (ORR) with safety (REFLECT trial) [12]. The REFLECT trial was an open-label, phase 3, multicenter trial that recruited patients with unresectable HCC who had not received treatment for advanced disease. Lenvatinib has been approved in Japan for unresectable HCC since March 23, 2018. This is the first approval worldwide. However, the efficacy and safety profile of lenvatinib are unknown in the real-world setting, including after sorafenib therapy.

The present study aimed to examine the efficacy and safety of lenvatinib in patients with advanced HCC in a real-world setting.

Materials and methods

Study design and population

This was a retrospective, multicenter, observational study. A total of 16 consecutive patients who had unresectable HCC, and were treated with lenvatinib from March 2018 to April 2018 were potentially eligible for the study. The inclusion and exclusion criteria were based on the REFLECT trial [12]. Eligible patients had measurable target lesion based on the modified Response Evaluation Criteria in Solid Tumors (m-RECIST) [13], Barcelona Clinic Liver Cancer stages B or C categorizations [14], Child–Pugh class A, and an Eastern Cooperative Oncology Group performance status score of 0 or 1 [15–17]. Included patients also had controlled hypertension and adequate liver and bone marrow functions. However, in this real-world clinical study, patients who had previously received sorafenib treatment, patients under maintenance dialysis, and patients with low platelet counts were also allowed.

Protocol

Patients received oral lenvatinib (Eisai Co., Ltd., Tokyo, JAPAN) 12 mg/day (for bodyweight > 60 kg) or 8 mg/day (for bodyweight < 60 kg). Dose interruptions followed by reductions for lenvatinib-related toxicities (to 8 mg/day, 4 mg/day, or 4 mg every other day) were permitted. Eisai Co., Ltd. prescribed protocols based on the results of the REFLECT trial [12]. Grades of adverse events (AEs) complied with the Common terminology criteria for adverse events (CTCAE) version 4.0 [18].

In cases of hypertension, when the systolic blood pressure (BP) was > 140 mmHg or the diastolic BP was > 90 mmHg, we continued with the administration using the same dosage; however, we also administered an antihypertensive agent. Despite antihypertensive therapy, when the systolic BP was > 160 mmHg or the diastolic BP was > 100 mmHg, lenvatinib was interrupted until the systolic BP became < 150 mmHg and diastolic BP was < 95 mmHg, and treatment with an antihypertensive agent was ensured. When resuming the administration of lenvatinib, the dose was reduced by one step. When Grade 4 side effects developed, administration was discontinued.

For hematologic toxicity and proteinuria, when Grade 3 side effects developed, lenvatinib was interrupted until the condition before the start of treatment or recovery to Grade 2 or lower was achieved. When administration was resumed, it was not reduced when the first side effect was shown; however, it was reduced by one step at the second and subsequent onset of side effects. When Grade 4 side effects developed, lenvatinib was interrupted until the condition before the start of treatment or recovery to Grade 2 or lower was achieved. When resuming with the administration, the dose was reduced by one step.

For other toxicities, when Grade 3 side effects developed, lenvatinib was interrupted until the condition before the start of treatment or recovery to Grade 1 or lower was achieved. When resuming the administration of lenvatinib, the dose was reduced by one step. When Grade 4 side effects developed, administration of the drug was discontinued.

Follow-up and outcome

Participants were observed for at least 12 weeks. Safety assessments were conducted by recording the vital signs, hematological and biochemical laboratory testing, urinalysis, and electrocardiography at 1, 2, 4, 8, and 12 weeks after the start of administration. AEs were graded according to the CTCAE version 4.0 [18]. Therapeutic effects were determined using m-RECIST [13] at the 8th week. The liver was examined with computed tomography or magnetic resonance imaging by the use of a triple-phase scanning technique. Baseline data on clinical parameters, adverse effects, lenvatinib dosages, tumor markers, and radiological findings were collected.

Statistical methods

The median was calculated for the clinical parameter values and the range was also reported.

Result

Patients' characteristics

A total of 16 patients with unresectable advanced HCC were included in this study from March 26, 2018, through April 30, 2018. All patients were observed until July 31, 2018. The median observation period was 115 (35–126) days. All cases were actual clinical cases with liver function of Child–Pugh A. All patients had prior treatment history, and a median of 3.9 (0.5–11.6) years had passed since the first treatment. Four cases that had previously received sorafenib treatment were included. In three of the four cases, inclusion in the study occurred after sequential treatment with sorafenib–regorafenib. A case of chronic renal failure undergoing maintenance dialysis was registered. Three cases with platelet counts of 75,000/μL or less were also included (Table 1).

AEs

AEs occurred in almost all patients (Table 2). Fatigue, hypertension, and proteinuria were identified as the AEs with the highest frequencies and were more than Grade 2. Fatigue of Grade 3 was observed in two of the four cases that had previously received sorafenib. Adjusted by patient-years, the AE rate was 27.3 episodes per patient-year. AEs of Grade 3 or higher occurred at a rate of 4.3 episodes per patient-year. AEs could be controlled by carrying out appropriate dose reduction, interruption, and symptomatic treatment according to the protocol. One elderly patient died of pneumonia.

Compliance

Treatment continued for 12 weeks in all cases except in one case of progressive disease (PD) and three cases of withdrawal due to AEs (a case of Grade 5 pneumonia and two cases of Grade 3 fatigue) (Fig. 1). In 12 weeks of observation, AEs led to lenvatinib drug interruption in 12 (75%) patients and dose reduction in 10 (63%). The mean lenvatinib dose intensity was 5.6 mg (70%) in the 8 mg/day group and 7.3 mg (61%) in the 12 mg/day group.

Treatment effects

The evaluation by m-RECIST at 8 weeks after the start of the treatment was possible in all cases except one (unevaluable due to Grade 5 AE). In the m-RECIST evaluation, 0, 6, 8, and 1 patients achieved complete response, partial response (PR), stable disease (SD), and PD, respectively (Fig. 2). The ORR was 40%, and the disease control rate was 93%. In the four cases that had been previously treated with sorafenib, one achieved PR and the remaining three were classified as SD.

Table 1 Patient characteristics

Feature	$N=16$
Gender (male: female)	12:4
Age, (years) (median range)	73 (61–92)
Body weight, (kg) (median range)	60 (37–83)
ECOG PS (0:1)	6:10
Previous treatment (yes: no)	16:0
Time from first treatment, (years) (median range)	3.9 (0.5–11.6)
Previous sorafenib treatment (yes: no)	4:12
Previous regorafenib treatment (yes: no)	3:13
Etiology (HBV:HCV:NBNC)	2:5:9
Child–Pugh Score (5:6)	10:6
AST, IU/L (median range)	43 (9–138)
ALT, IU/L (median range)	38 (6–129)
Platelets, $\times 10^4$/μL (median range)	13.3 (4.8–33.6)
NH_3, (μg/dL) (median range)	48.3 (11–112)
Vascular invasion (portal vein: hepatic vein: bile duct)	4:1:0
AFP, (ng/mL) (median range)	18.3 (1.8–2,974,644)
AFP-L3, (%) (median range)	13.9 (0.5–73.8)
PIVKA-II, (mAU/mL) (median range)	374 (13–64,900)

ECOG PS Eastern Cooperative Oncology Group performance status, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *NBNC* non B non C, *AST* aspartate transaminase, *ALT* alanine aminotransferase, *AFP* alpha-fetoprotein, *AFP-L3* Lens culinaris agglutinin-reactive α-fetoprotein isoform, *PIVKA-II* protein induced by vitamin K absence or antagonist-II

Table 2 Adverse events

Adverse events	G1	G2	G3	G4	G5	Total
Fatigue	1	3	8			12
Hypertension	1	7	2			10
Decreased appetite	1	8				9
Diarrhea	6	2				8
Hypothyroidism		8				8
Proteinuria		3	4			7
Palmar-plantar erythrodysesthesia	3	2				5
Dysphonia	5					5
Epistaxis	4					4
Fever	3					3
Edema		3				3
Cramps	1	1				2
Hypoalbuminemia		2				2
Ascites		2				2
Nausea		2				2
Dysgeusia		2				2
Pneumonia		1			1	2
Abdominal distension		1				1
Pruritus	1					1
Mucositis oral	1					1
Oral hemorrhage	1					1
Chills	1					1
Urinary tract infection	1					1
Increased blood bilirubin			1			1
Rash	1					1
Oral dysesthesia	1					1
Eczema		1				1
Alopecia	1					1
Urinary stone		1				1
Urinary frequency	1					1
Abdominal pain	1					1
Constipation	1					1
Arthritis		1				1

G Grade

Discussion

We have shown the efficacy and safety of lenvatinib for patients with advanced HCC in a real-world setting. Safety profiles at 12 weeks and efficacy at 8 weeks after the start of treatment of lenvatinib were observed. Recently Hiraoka et al. [19] also reported their experience with lenvatinib in a real-world setting. However, in 35% of their patients, the observation period was only 14 days, and the average of the entire cohort was 31 days. Our study is the first to report treatment results in a real-world setting with a sufficient observation period.

It is necessary to determine how patients in actual clinical practice respond to a new treatment as these populations can differ from patients included in a phase 3 trial. In term of patient characteristics, all of the eligible patients in our study had prior treatment history, including some patients who had received sorafenib–regorafenib sequential therapy, and a median of 3.9 (0.5–11.6) years had passed since the first treatment. In contrast, 32% of the patients in the REFLECT trial for lenvatinib had no previous anticancer therapy. Moreover, patients in this study were older (73 years old vs. 63 years old) and more had a lower body weight (< 60 kg: 56% vs. 32%) than those in the REFLECT trial [12]. A previous report [19] in a Japanese cohort showed similar trends, suggesting that elderly age and low body weight may be characteristics of the Japanese HCC patient population.

In 12 weeks of observation, AEs were observed in almost all patients. The safety profile was consistent with those in previous studies [12, 19–22]. However, in this

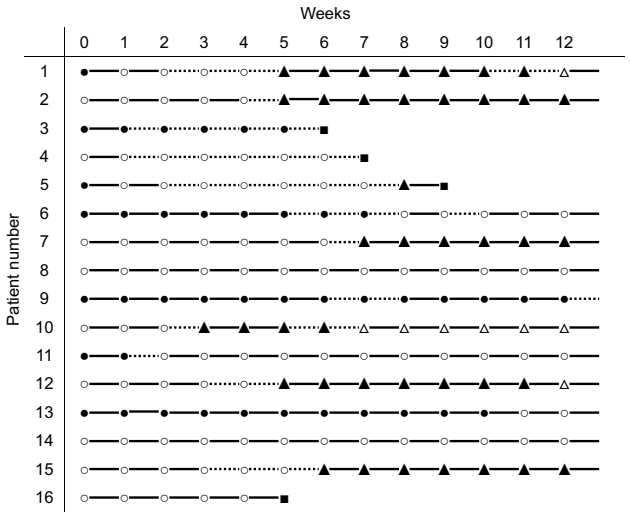

Fig. 1 Clinical course. Closed circle: 12 mg, open circle: 8 mg, closed triangle: 4 mg, open triangle: 4 mg every other day, closed square: withdrawal, line: administration, dotted line: interruption. Treatment continued for 12 weeks in all cases except for one case of progressive disease and three cases of adverse event. Lenvatinib treatment could be continued by carrying out appropriate dose reduction, interruption, and symptomatic treatment according to the protocol

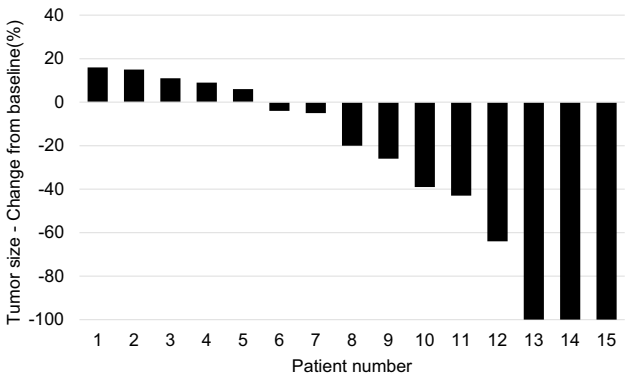

Fig. 2 Tumor reduction rate in target lesion by m-RECIST at 8 weeks. The evaluation by m-RECIST at 8 weeks after the start of the treatment was evaluable in all cases except for one case. In the evaluation by m-RECIST, these were 0, 6, 8, and 1 cases of CR, PR, SD, and PD, respectively. Tumor markers were not completely within the normal range; therefore, there was no CR. *m-RECIST* modified Response Evaluation Criteria in Solid Tumors, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

real-world clinical study, The AE rate was higher than that in the REFLECT trial (episodes per patient-year, 27.3 vs. 18.9) [12]. Furthermore, the rate of AEs of Grade 3 or higher was also higher in this study (episodes per patient-year, 4.3 vs. 3.2). Because of the higher rate of AEs, the drug interruption (75% vs. 40%), dose reduction (63% vs. 37%), and drug withdrawal (19% vs. 7%) were higher than those in the REFLECT trial [12]. The mean dose intensity in the 8 mg/day group was 5.6 mg (70%) compared to 7.0 mg (88%) in the REFLECT trial, and that in the 12 mg/day group was 7.3 mg (61%) compared to 10.5 mg (88%) in the REFLECT trial [12]. However, AEs could be controlled according to the protocol. Differences in patient background such as treatment experience, time from first treatment, age and weight may have been the cause of the high incidence of AEs.

Since the observation period was short, it was impossible to correctly evaluate the therapeutic effect. However, in the evaluation by m-RECIST at 8 weeks after the initiation of treatment, the number of patients achieving PR, SD, and PD were 6, 8, and 1, respectively. The ORR was 40.0% in this study vs. 40.6% in the REFLECT trial [12]. A similar ORR (40.7%) which was evaluated by m-RECIST at 4 weeks after the start of lenvatinib was also obtained in the previous report in the Japanese cohort [19]. It is a promising result of the therapeutic effect although further follow-up observation is necessary. Although the observation period is short, the tumor shrinkage effect was actually observed in some cases. The possibility of conversion therapy in cases achieving partial response can also be expected [23]. If conversion therapy can actually be performed, further prognosis improvement can be expected.

The AE rate was similar in patients who had received sorafenib–regorafenib sequential therapy and patients who had not. In cases where Child–Pugh A liver function can be maintained, lenvatinib has potential as a third-line treatment after sorafenib–regorafenib sequential therapy.

A limitation of our study is that the number of cases was limited. Moreover, our parameters such as Japanese ethnicity, increased age, and low body weight can be confounders. Another confounding factor is that there were various pretreatment histories, including sorafenib–regorafenib sequential therapy, in all eligible patients. Another limitation of our study is that the observation period was short. However, this analysis was necessary as an evaluation of the initial safety and efficacy in clinical practice. In the future, large-scale analysis with an increased number of cases and sufficient observation period is necessary.

In conclusion, we have shown the efficacy and safety of lenvatinib for patients with advanced HCC in a real-world setting. Lenvatinib treatment for HCC could be accomplished with safety and good response.

Compliance with ethical standards

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent Informed consent was obtained from all patients for being included in the study. All relevant institutional review boards approved the study.

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