Evaluation of the therapeutic effects and tolerability of modified lenvatinib administration methods for unresectable hepatocellular carcinoma: A preliminary study

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Abstract. Lenvatinib (LEN), a multitarget tyrosine kinase inhibitor, is a standard therapeutic agent for hepatocellular carcinoma, but the high incidence of adverse events (AEs) related to LEN treatment often necessitates treatment discontinuation. The present study aimed to clarify the therapeutic efficacy and tolerability of modified LEN dosing methods, such as alternate-day dosing, necessitated by AEs of LEN. A total of 66 patients who received LEN at Ogaki Municipal Hospital (Ogaki, Japan) between April 2018 and January 2022 were retrospectively evaluated. These patients were divided into those who completed treatment with the standard administration method (standard LEN, n=48) and those who changed from the standard administration method to a modified administration method in the middle of treatment [modified LEN (weekends off/alternate days), n=18]. The treatment duration and reasons for discontinuation of LEN treatment were analysed. The discontinuation rate due to AEs in the modified LEN group (1 patient) was less compared with that in the standard LEN group (16 patients) (P=0.022). The median treatment duration for patients in the standard LEN (n=48), modified LEN (weekends off, n=6) and modified LEN (alternate days, n=12) groups was 71 [95% confidence interval (CI) 55-134], 483 (95% CI: 193-644) and 222 (95% CI: 98-303) days, respectively (P=0.044). Modification of the administration method ensured fewer AE-related treatment discontinuations. However, weekends off dosing showed a longer treatment duration compared with standard dosing, whereas alternate day dosing showed no difference from standard dosing.

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Abbreviations: AE, adverse event; CI, confidence interval; LEN, lenvatinib; RDI, relative dose intensity

Key words: adverse event, duration of treatment, hepatocellular carcinoma, ingenuity of administration method, lenvatinib, unresectable

Introduction

Lenvatinib (LEN) is a multitarget tyrosine kinase inhibitor that can target vascular endothelial growth factor receptors 1, 2, and 3, fibroblast growth factor receptors 1 through 4, platelet-derived growth factor receptor α, rearranged during transfection (RET), and stem cell factor receptor (KIT). Moreover, LEN also inhibits the formation of vessel-like luminal structures of vascular endothelial cells induced by VEGF and FGF. The recommended dose of LEN is usually 12 mg/day for those weighing ≥60 kg and 8 mg/day for those weighing <60 kg, administered orally once a day.

LEN is a standard therapeutic agent for hepatocellular carcinoma, but the high incidence of adverse events (AEs) is a problematic aspect of LEN treatment (1-4), since these AEs may necessitate treatment discontinuation. Rash and diarrhea are common side effects of tyrosine kinase inhibitor (TKI) therapy administered to patients with non-small cell lung cancer (5). The most common any-grade AEs of LEN are hypertension (42%), diarrhoea (39%), decreased appetite (34%), decreased weight (31%), and fatigue (30%) (2). Iwamoto reported that the incidence rates of any grade and grade ≥3 AEs were 82.1 and 49.6%. Fatigue is the most important AE because it can result in dose reduction and discontinuation (4).

Although the LEN dose can be tapered in cases with severe AEs, the lowest dose is 4 mg/day. Therefore, in clinical practice, if the dose is to be further reduced for treatment continuation, modified administration methods such as taking the drug for 5 days with 2-day intervals (weekends off) may have to be applied. Iwamoto *et al* reported the tolerability and therapeutic effects of weekends off administration (4), and in their study, of the 30 patients who received weekends off LEN, 66.7% had tolerable AEs. Thus, weekends off administration significantly prolongs the administration period and survival (4). In actual clinical practice, other modified administration methods such as administration every other day may also be performed depending on the patient's condition. However, the benefit of administration every other day has not

Table I. Patient characteristics.

Characteristic	Standard LEN	Modified LEN (weekends off)	Standard LEN (alternate day)	P-value
Patients, n	48.0	6.0	12.0	
Age, years				
Median (range)	73.0 (48.0-86.0)	76.0 (74.0-87.0)	76.0 (69.0-88.0)	0.441[a]
Sex, n				
Male	43.0	5.0	11.0	0.811[b]
Female	5.0	1.0	1.0	
Height, cm				
Median (range)	161.0 (144.0-173.0)	162.0 (158.0-166.0)	160.0 (158.0-182.0)	0.950[a]
Weight, kg				
Median (range)	60.0 (41.0-98.0)	55.0 (40.0-79.0)	69.0 (54.0-84.0)	0.028[a,c]
Body surface area, kg/m^2				
Median (range)	1.6 (1.2-2.0)	1.6 (1.4-1.9)	1.7 (1.6-2.1)	0.043[a,c]
Creatinine clearance, ml/min				
Median (range)	69.7 (35.3-131.6)	56.9 (37.7-73.6)	68.0 (39.0-93.9)	0.320[a]
Cause of hepatocellular carcinoma, n				0.590[b]
Hepatitis B virus	7.0	0.0	2.0	
Hepatitis C virus	16.0	4.0	3.0	
Non-B non-C	25.0	2.0	7.0	
Performance status, n				0.936[b]
0	31.0	4.0	7.0	
1	15.0	2.0	4.0	
2	2.0	0.0	1.0	
Past history of transcatheter arterial chemoembolization, n				
Yes	38.0	5.0	10.0	0.930[b]
Child-Pugh, n				
A	29.0	4.0	6.0	0.709[b]
B	19.0	2.0	6.0	

[a]Kruskal-Wallis test. [b]Fisher's exact probability test. [c]P<0.05.

been reported. Therefore, analyses of LEN dosage and reasons for discontinuation due to AEs and clarifying the usefulness of these administration methods will facilitate AE management in the future.

The purpose of this study is to clarify the therapeutic efficacy and tolerability of LEN administered with a modified dosing method such as alternate day dosing due to AEs.

Patients and methods

Patients and evaluations. A total of 66 patients treated with LEN as the first-line treatment for hepatocellular carcinoma at Ogaki Municipal Hospital (Ogaki, Japan) between April 2018 and January 2022 were retrospectively evaluated. The LEN-administered patients were divided into those who completed treatment with the standard administration method (standard LEN) and those who changed from the standard administration method to a modified method in the middle of treatment [modified LEN (weekends off/alternate days)]. We analysed patient characteristics, treatment duration, AEs, relative dose intensity (RDI), and LEN-related reasons for discontinuation over the treatment duration. The data were analysed using electronic charts and pharmacy service records. AEs were evaluated according to the Common Terminology Criteria for Adverse Events, version 5.0 (6), and the most severe grades during chemotherapy were reported. Personal information was protected in the aggregated data. This study was approved by the Institutional Review Board of Ogaki Municipal Hospital (Ogaki, Japan; approval number: 20221124-16). The need for informed consent was waived because of the retrospective nature of the study.

Treatment protocol. The dose of LEN was based on body weight: the initial dose was 12 mg/day for those weighing ≥60 kg and 8 mg/day for those weighing <60 kg. During

28-day cycles, dose adjustment was allowed for lenvatinib based on adverse events with reduction to 8 mg or 4 mg per day, 4 mg every other day, and interruption (2,7). For patients with Child-Pugh B disease, the initial dose was reduced from 12 to 8 mg once daily. In patients experiencing unacceptable drug-related AEs, the LEN dose was reduced or treatment was interrupted in accordance with the instructions provided by the manufacturer. Dose reduction or temporary interruption of LEN was maintained until the AEs resolved to grade 1 or 2. When continuing administration at a reduced dose, the dose was reduced to 20, 14, 10, 8, or 4 mg once daily.

Statistical analysis. Between-group comparisons were performed using the *F*-test. Kruskal-Wallis test, Fisher's exact probability tests were used to compare patient characteristics, AEs and reasons for discontinuation. Fisher's PLSD were used to compare RDI. Kaplan-Meier and log-rank tests followed by the Bonferroni correction were used to compare treatment durations. Differences were considered statistically significant at $P<0.05$. All analyses were performed using EZR software (version 1.30, Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R software (The R Foundation for Statistical Computing, Vienna, Austria) (8).

Results

Patient characteristics. The standard and modified LEN groups (weekends off/alternate days) included 48 and 18 (6/12) patients, respectively. Patient characteristics are summarised in Table I. Patient background in weight and body surface area did differ significantly between the standard, modified LEN (weekends off), and modified LEN (alternate days) groups.

Reasons for discontinuation. Discontinuations due to AEs in the modified LEN group (1 of 18 patients) were fewer than those in the standard LEN group (16 of 48 patients, P=0.022). Discontinuations due to progressive disease (PD) in the modified LEN group (9 of 18 patients) were more than those in the standard LEN group (11 of 48 patients, P=0.032). The reasons for discontinuation in the standard and modified LEN groups are summarised in Table II. The two groups showed no significant differences in deterioration in performance status, or deterioration of condition.

AEs leading to treatment discontinuation and the doses at the time of discontinuation. The AEs leading to treatment discontinuation and the LEN doses at the time of discontinuation are summarised in Table III. In the modified LEN group, treatment was discontinued due to abnormal urinary protein levels during administration of alternate day dosing at 4 mg/day (1 case). In the standard LEN group, 10 of the 16 patients (62.5%) who discontinued treatment due to AEs were receiving LEN at 4 mg/day. The reasons for discontinuation in the standard LEN group when receiving 4 mg/day were fatigue (three cases), anorexia (four cases), abnormal urinary protein levels (two cases), nausea/vomiting (one case), fullness (one case), disorientation (one case), and hoarseness (one case). On the other hand, six of the 16 patients (37.5%) discontinued treatment while receiving 8 mg/day or 12 mg/day.

The effects of lenvatinib treatment on the treatment duration. Kaplan-Meier survival curves according to the duration of treatment with LEN for all patients are shown in Fig. 1. The

Table II. Reasons for discontinuation at lenvatinib treatment.

Events	Modified LEN (n=18)	Standard LEN (n=48)	P-value
Adverse events	1	16	0.022[a]
Progressive disease	9	11	0.032[a]
Deterioration in performance status	2	8	0.566
Deterioration of condition	3	6	0.660
Others	2	4	0.704
Ongoing	1	3	0.916

[a]P<0.05. LEN, Lenvatinib.

Table III. Adverse events and dose leading to treatment discontinuation during LEN treatment.

A, Modified LEN	
Dose	Adverse events
Alternate-day dosing with 4 mg/day	Urinary protein
B, Standard LEN	
Dose	Adverse events
12 mg/day every day	Rash
8 mg/day every day	Stomachache
8 mg/day every day	Anorexia
8 mg/day every day	Hypothyroidism/slight fever/rash
8 mg/day every day	Nausea
8 mg/day every day	Anorexia/fatigue
4 mg/day every day	Fullness/fatigue
4 mg/day every day	Urinary protein
4 mg/day every day	Fatigue/anorexia
4 mg/day every day	Anorexia/hoarseness
4 mg/day every day	Nausea/vomiting
4 mg/day every day	Urinary protein
4 mg/day every day	Anorexia
4 mg/day every day	Anorexia
4 mg/day every day	Disorientation
4 mg/day every day	Fatigue

LEN, Lenvatinib.

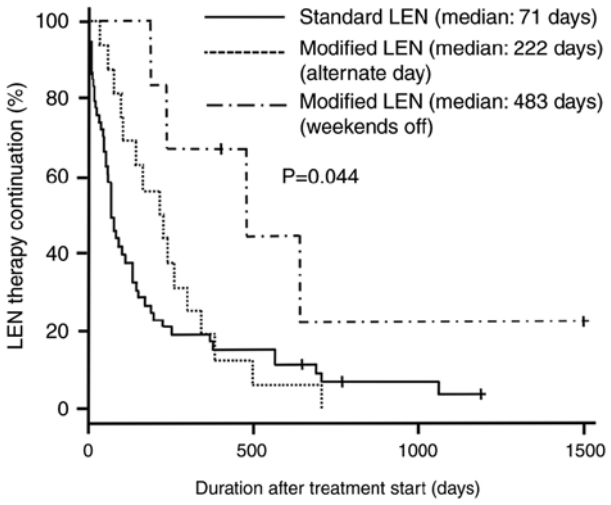

Figure 1. Kaplan-Meier survival curves according to treatment with LEN for all patients. Kaplan-Meier analysis of hepatocellular carcinoma patients who received LEN treatment stratified by administration methods, and difference were evaluated using the log-rank test. LEN, lenvatinib. (Standard LEN vs. modified LEN (Weekends off) log-rank test, P=0.012; Standard LEN vs. modified LEN (Alternate day) log-rank test, P=0.234; modified LEN (Weekends off) vs. modified LEN (Alternate day) log-rank test, P=0.019).

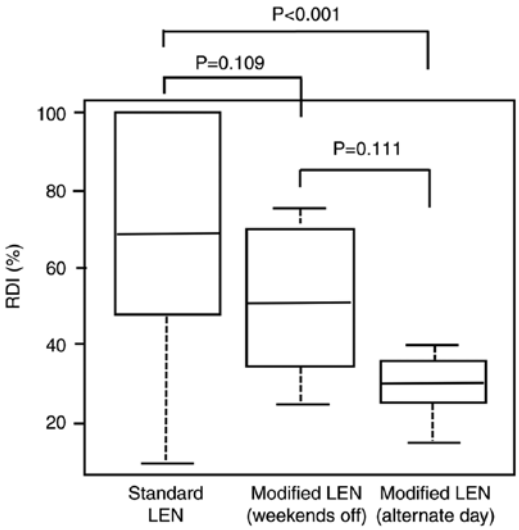

Figure 2. RDI of LEN in the standard and modified LEN administration groups (weekends off/alternate days). LEN, lenvatinib; RDI, relative dose intensity.

median treatment duration for patients in the standard LEN (n=48), modified LEN (weekends off, n=6), and modified LEN (alternate days, n=12) groups was 71 (95% confidence interval [CI]: 55-134), 483 (95% CI: 193-644), and 222 (95% CI: 98-303) days, respectively (log-rank test, P=0.044).

RDI of lenvatinib in the treatment groups. The RDI of LEN for the standard LEN and modified LEN groups are shown in Fig. 2. The median RDI in the standard LEN (n=48), modified LEN (weekends off, n=6), and modified LEN (alternate days, n=12) groups was 68.5% (95% CI: 46.3-100%), 50.0% (95% CI: 32.5-71.2%), and 30.0% (95% CI: 25.0-35.0%), respectively. The median RDI in the modified LEN (alternate days) group was lower than that in the standard LEN group (P<0.001).

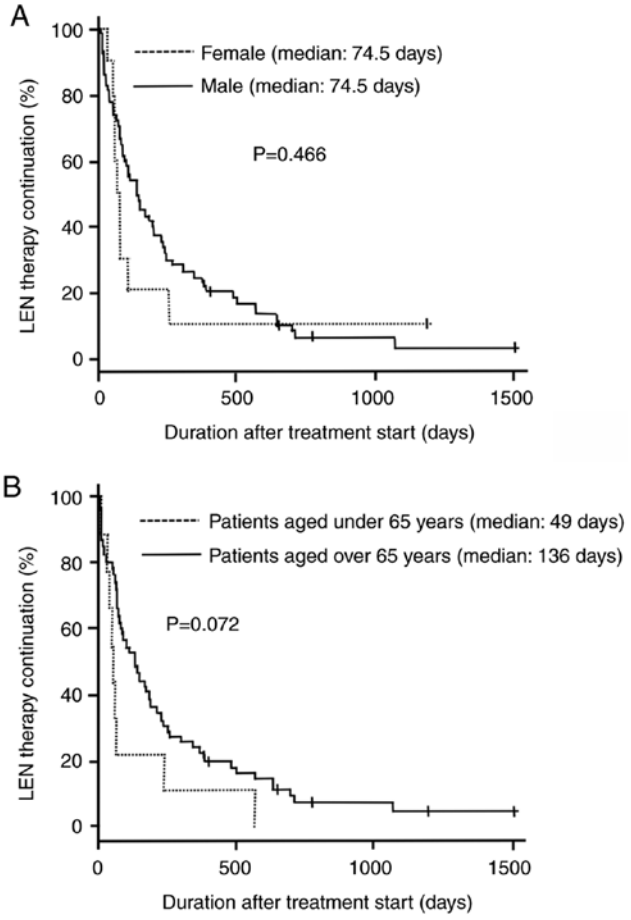

Figure 3. Kaplan-Meier survival curves by age or sex by duration of treatment with LEN. (A) Kaplan-Meier survival curves of sex by duration of treatment with LEN; (B) Kaplan-Meier survival curves of age (65 years) by duration of treatment with LEN. LEN, lenvatinib.

Analysis of the effects depending on age and sex. Kaplan-Meier survival curves by age (65 years) or sex by duration of treatment with LEN are as follows. The median duration of treatment for patients aged over 65 years (n=57) and under 65 years (n=9) groups were 136 (95% CI: 80-193) and 49 (95% CI: 9-241) days, respectively (log-rank test, P=0.072). The median duration of treatment for patients in female (n=7) and male (n=59) groups were 66.5 (95% CI: 28-98) and 136.0 (95% CI: 80-196) days, respectively (log-rank test, P=0.466) (Fig. 3).

Discussion

This study clarified the therapeutic effects and tolerability of AEs with modified LEN administration methods such as alternate day administration. Modification of the administration method ensured fewer AE-related treatment discontinuations. However, weekends off dosing showed in a longer treatment duration than standard dosing, whereas alternate day dosing showed no difference from standard dosing.

In the REFLECT study, fatigue and anorexia frequently occurred from the beginning of administration (2). Among AEs leading to discontinuation of LEN, Iwamoto *et al* reported that fatigue was the most important because it led to dose reduction and discontinuation (4). Moreover, Katsuragawa *et al* reported that in patients taking LEN for hepatocellular carcinoma,

fatigue and anorexia are often responsible for discontinuation of administration (9). Similar to these reports, the present study showed that fatigue and anorexia were the most common AEs that led to discontinuation. The number of discontinuations due to AEs in the modified LEN group was lower (1 of 18) than that in the standard LEN group (16 of 48), suggesting that AE-related discontinuations can be prevented by devising an appropriate administration method. Modified LEN had more discontinuations due to PD than standard LEN. This may be caused by the increased PD discontinuations due to reduced discontinuations because of the side effects with modified LEN.

In our analyses of the AEs leading to treatment discontinuation and the doses at the time of discontinuation, one patient in the modified LEN group discontinued treatment due to AEs despite receiving 4 mg every other day. In contrast, 10 of the 16 patients (62.5%) in the standard LEN group who discontinued treatment due to AEs were administered 4 mg/day. Thus, in the standard LEN group, if treatment continuation was difficult due to AEs at a dose of 4 mg/day, treatment could be continued by modifying the dosing method, e.g., by administering 4 mg every other day. In the standard LEN group, the remaining six of the 16 patients (37.5%) who discontinued treatment due to LEN were receiving treatment at 8 mg or 12 mg. Thus, it is conceivable that treatment could be continued by further dose reduction or drug interruption. This finding highlights the importance of AE management, including prompt dose reduction and changes in the administration method. However, in terms of treatment duration, alternate day dosing resulted in fewer treatment withdrawals due to AEs than standard dosing, but the treatment duration remained the same. However, weekends off dosing resulted in a significantly longer treatment duration than standard dosing, indicating that alternate day administration was insufficient in terms of efficacy. Iwamoto *et al* reported that the weekend administration method significantly extends the administration period and survival rate (4).

In our assessments of the RDI of LEN during the treatment period, the RDI in the alternate day dosing group was lower than that in standard administration group. However, no difference in RDI was observed between standard dosing and weekends off dosing. To derive the optimal therapeutic benefit of LEN in anticancer drug therapy, adequately manage of AEs during LEN therapy and maintain RDI is important (10). In addition, a higher RDI is associated with better overall survival and progression-free survival as factors affecting the continuation of LEN treatment (11-14). In this study, there was no difference in treatment duration between alternate-day administration and standard administration, suggesting that the RDI results indicate that the therapeutic effect is low if the RDI is below a certain level. Based on these findings, we consider that if the RDI is too low, the treatment duration cannot be prolonged. However, for sorafenib, a multikinase inhibitor similar to LEN, the presence of HFS or diarrhoea may be relevant factors predicting longer overall survival in patients with advanced hepatocellular carcinoma (15-17). Therefore, early identification and control of these reactions are important for continued sorafenib therapy (15-17). Specifically, we considered that even if the RDI is high, if treatment is discontinued because of AEs, it will lead to a shortened duration of treatment and may affect survival.

To facilitate the management of AEs in patients receiving LEN for liver cancer, we would like to emphasise some aspects of the study: First, the dose of LEN was tapered due to AEs, but the lowest dose was maintained at 4 mg. Therefore, in the clinical setting, patients should be explained that AEs can be tolerated and treatment can be continued by devising a modified dosing method such as weekends off dosing. Second, Ogushi *et al* reported that Child-Pugh B patients require dose reduction due to grade 2 AEs and show less tolerability to these AEs than Child-Pugh A patients (3). Therefore, special care should be taken in the management of Child-Pugh B patients.

The study limitations included the relatively short observation period, the limited sample, and the retrospective, single-centre nature of the study. Because of the small sample size, this study may not have had sufficient statistical power to yield accurate estimates. In some cases, we were unable to capture information on tumour size, so we were unable to analyse treatment response (PD, stable disease, partial response). Future studies should aim to address this limitation. Moreover, we recommend calculating the effective RDI when determining the administration method. Although overall survival (OS) was not examined in this study, it would be desirable to clarify the relationship between reasons for treatment discontinuation and OS.

In the future, to demonstrate the therapeutic effects of LEN, adequate management of AEs by appropriately modifying the timing and duration of treatment will be an important consideration. Among the management approaches, devising an administration method to prevent treatment discontinuation owing to AEs is considered useful.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

MK contributed to the study design, collected and provided the data, was the principal author of the report and was the guarantor of the article and all data. MG, SY, HA, EU and TY contributed to the study design, reviewed the article, and supervised the drafting of the report and submission process. All authors approved the final version of the manuscript. MG, SY and HA confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Ogaki Municipal Hospital (Ogaki, Japan; approval

no. 20221124-16). The requirement for obtaining informed consent was waived due to the retrospective study design.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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