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# Impact of Relative Dose Intensity of Early-phase Lenvatinib Treatment on Therapeutic Response in Hepatocellular Carcinoma

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**Abstract.** *Background: Factors associated with response to lenvatinib have not been clarified in patients with hepatocellular carcinoma (HCC). Patients and Methods: This study retrospectively analyzed 50 patients treated with lenvatinib as first-line therapy between March 2018 and March 2019. Patients were divided into two groups by the Modified Response Evaluation Criteria in Solid Tumours (mRECIST) (responders and non-responders, whose best overall responses were complete (CR)/partial response (PR) and stable (SD)/progressive disease (PD), respectively). Factors associated with response were assessed, including the relative dose intensity 8 weeks after lenvatinib induction (8W-RDI). Results: The best overall responses were 0/22/14/14 of CR/PR/SD/PD. Multivariate analysis revealed that only 8W-RDI was significantly associated with response. The receiver operating characteristic curve for 8W-RDI in differentiating responders from non-responders revealed a cut-off value of 75%. Patients with 8W-RDI ≥75% experienced a higher response rate and longer progression-free survival than patients with 8W-RDI <75%. Conclusion: Our results suggest that maintaining an RDI ≥75% during the initial 8 weeks of lenvatinib treatment has a favorable impact on response.*

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*Key Words:* Hepatocellular carcinoma, lenvatinib, dose intensity, objective response.

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide and the second leading cause of cancer-related death, resulting in more than 700,000 deaths

Table I. *Patient characteristics*.

| Variable | | Total (n=50) | Responders (n=22) | Non-responders (n=28) | *p*-Value |
|---|---|---|---|---|---|
| Age, years | Median (range) | 78 (53-93) | 70 (53-86) | 79 (57-93) | **0.075** |
| Gender, n | Male/female | 38/12 | 19/3 | 19/9 | 0.186 |
| ECOG PS, n | 0/1/2 | 37/12/1 | 17/5/0 | 20/7/1 | 0.648 |
| Body weight, n | <60/≥60 kg | 33/17 | 13/9 | 20/8 | 0.386 |
| Etiology, n | HBV/HCV/alcohol/other | 9/18/8/15 | 5/8/3/6 | 4/10/5/9 | 0.868 |
| Child–Pugh score, n | 5/6/7 | 30/17/3 | 17/5/0 | 13/12/3 | **0.056** |
| ALBI grade, n | 1/2 | 18/32 | 9/13 | 8/20 | 0.386 |
| EHS, n | Yes/no | 13/37 | 9/13 | 4/24 | 0.051 |
| MVI, n | Yes/no | 8/42 | 3/19 | 5/23 | 0.715 |
| AFP, ng/ml | Median (range) | 90.1 (2.1-185,772) | 24.5 (2.8-25,881) | 384 (2.1-185,772) | **0.097** |
| PIVKA II, mAU/ml | Median (range) | 540.5 (11.0-316,000) | 164.5 (24-14,161) | 868 (11-316,000) | **0.051** |
| Prior TACE history, n | Yes/no | 38/12 | 17/5 | 21/7 | >0.99 |
| Initial dose of LEN, n | Full/reduced | 45/5 | 21/1 | 23/4 | 0.362 |
| 8W-RDI, % | Median (range) | 74 (8-100) | 100 (42.4-100) | 48.2 (8-100) | **<0.001** |

ECOG: Eastern Cooperative Oncology Group; PS: performance status; HBV: hepatitis B virus; HCV: hepatitis C virus; ALBI: Albumin-Bilirubin; EHS: extrahepatic spread; MVI: macrovascular invasion; AFP: alpha-fetoprotein; PIVKA-II: protein induced by vitamin K absence or antagonist-II; TACE: transarterial chemoembolization; LEN: lenvatinib; 8W-RDI: relative dose intensity 8 weeks after lenvatinib induction. Bold font for indicates p-values of less than 0.1, for factors which were subsequently included in the multivariate analysis.

annually (1, 2). Only 40% of patients with HCC are diagnosed with early-stage disease, and even after successful early treatment, most patients experience disease recurrence; thus, almost half of all patients ultimately receive systemic therapies (3, 4).

Lenvatinib is an oral multi-target tyrosine kinase inhibitor (TKI) that has anti-angiogenic and antiproliferative effects. In the phase III REFLECT trial, lenvatinib was found to be non-inferior to sorafenib in terms of overall survival (OS) in patients with advanced HCC and has become available as a therapy in first-line setting for unresectable HCC (5). The response rate to lenvatinib according to the Modified Response Evaluation Criteria in Solid Tumours (mRECIST) (6) was significantly higher than that for sorafenib (40.6% *vs.* 12.4%, respectively). More recently, a post-hoc analysis of the REFLECT trial reported that objective response (OR) by mRECIST was an independent predictor of OS and the median OS was 22.4 months for responders and 11.4 months for non-responders (7). The correlation between OR by mRECIST and OS has also been demonstrated for other targeted therapies (*e.g.* brivanib, nintedanib, and sorafenib) based on data from prospective randomized trials on HCC (8-10). Furthermore, if these drugs are effective, a greater choice of additional therapies, such as conversion hepatectomy, become available (11, 12). According to these reports and the high response rate to lenvatinib, the purpose of systemic chemotherapy in unresectable HCC is changing from controlling disease to yielding favorable responses. Therefore, in order to identify factors associated with OR to lenvatinib therapy is becoming increasingly crucial.

The relative dose intensity (RDI) is the ratio of the actual dose intensity of chemotherapy delivered to the standard recommended dose intensity (13). Several studies have demonstrated a correlation between RDI, particularly in the early phase of treatment, and survival in patients with various malignancies, such as renal cell carcinoma, gastrointestinal stromal tumor, soft-tissue sarcoma, and chronic myeloid leukemia treated with TKIs (14-17). However, to our knowledge, no studies have investigated the association between RDI and therapeutic efficacy in patients with HCC treated with TKIs. Indeed, patients receiving lenvatinib therapy, particularly in real-world settings, often undergo dose modifications due to several factors, including adverse events (AEs), reduced liver function, and deterioration of Eastern Cooperative Oncology Group performance status (ECOG PS) (18, 19). Thus, the dose–response relationship is of critical concern. The aim of this study was to evaluate the impact of RDI during the early phase of lenvatinib treatment on therapeutic response in patients with HCC.

## Patients and Methods

*Study design and patients*. This was an observational, retrospective, multicenter study focused on patients with HCC treated with lenvatinib in routine clinical practice. From March 2018 to March 2019, lenvatinib was administered to 105 Japanese patients at 16 institutions in Japan [Kyoto Prefectural University of Medicine (n=26), Omihachiman Community Medical Center (n=14), Japanese Red Cross Kyoto Daiichi Hospital (n=12), Saiseikai Suita Hospital (n=11), North Medical Center of Kyoto Prefectural University of Medicine (n=10), Osaka General Hospital of West Japan Railway

Company (n=8), Matsushita Memorial Hospital (n=4), Otsu City Hospital (n=4), Kyoto Yamashiro General Medical Center (n=3), Fukuchiyama City Hospital (n=3), Koseikai Takeda Hospital (n=2), Akashi City Hospital (n=2), Japanese Red Cross Kyoto Daini Hospital (n=2), Kyoto City Hospital (n=2), Saiseikai Kyoto Hospital (n=1), and Kyoto Chubu Medical Center (n=1)]. Of these patients, 69 were given lenvatinib as first-line systemic treatment. Of these, after patients with a short observation period (<8 weeks) or those with lacking data were excluded, 50 patients were enrolled in the present study. They were divided into two groups, responders (n=22) and non-responders (n=28), based on whether their best overall responses were complete (CR)/partial (PR) response or stable (SD)/progressive (PD) disease, respectively. Data were obtained from clinical medical records with a cut-off date of March 31, 2019. This study was conducted in accordance with the Declaration of Helsinki. This study protocol was approved by the institution's Human Research Committees.

*Diagnosis and treatment*. The diagnosis of HCC was based on imaging results (20) and elevated serum level of alpha-fetoprotein (AFP) or protein induced by vitamin K absence or antagonist-II (PIVKA-II). Patients received oral lenvatinib at 12 mg/day (for body weight ≥60 kg) or 8 mg/day (for body weight <60 kg), although lower starting doses were used in some cases based on physician judgement. Treatment was continued until tumor progression occurred or AEs impeding continuation developed. Dose modification due to AEs was allowed based on the treating physician's discretion. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (ver. 4.0) (21) and AEs resulting in treatment withdrawal, dose reduction, or drug interruption were defined as dose-limiting toxicities (DLTs). Radiological assessments using enhanced computed tomography or magnetic resonance imaging were performed at baseline and every 8 weeks thereafter by two hepatic physicians in our institutions (A.T and M.M.) in accordance with the mRECIST guidelines. A 'best overall response' was defined as the best response across all time points until PD during lenvatinib treatment.

*Relative dose intensity*. In order to investigate the impact of RDI during the early phase of treatment on the therapeutic efficacy of lenvatinib, we defined the initial 8-week RDI (8W-RDI) as early-phase dose intensity, consistent with the first evaluation period after initiation of lenvatinib therapy. 8W-RDI was defined as the ratio of the actual dose delivered during the initial 8 weeks to the standard dose (body weight ≥60 kg: 12 mg × 8 weeks; <60 kg: 8 mg × 8 weeks).

*Statistical analysis*. In order to clarify factors contributing to response, different clinical parameters were assessed, including age, gender, ECOG PS, body weight, Child–Pugh score, albumin–bilirubin (ALBI) grade (22), etiology, extrahepatic spread (EHS), macrovascular invasion, AFP, PIVKA-II, prior transarterial chemoembolization history, starting lenvatinib dose (full dose/reduced dose), and 8W-RDI. Univariate analyses were performed using Fisher's exact test and Mann–Whitney *U*-test, as appropriate. Multivariate analysis was performed by logistic regression analysis. The results were presented as odds ratio with 95% confidence intervals (CIs). A *p*-value of less than 0.05 was considered statistically significant. 8W-RDI cut-off values for predicting differences between responders and non-responders were calculated to produce receiver operating characteristic (ROC) curves. Progression-free survival (PFS) was estimated using the Kaplan–Meier method, comparing high with low 8W-RDI by log-rank test. Time to response was defined as the time from the initiation of lenvatinib to the date of OR achievement among responders. Statistical analyses were conducted using SPSS software Ver 25 (IBM, Armonk, NY, USA).

Table II. *Multivariate analyses of factors contributing to objective response to lenvatinib in patients with hepatocellular carcinoma.*

| | Multivariate analysis† | | |
|---|---|---|---|
| Factor | Odds ratio | 95% CI | *p*-Value |
| Age, per 1 year increment | 0.923 | 0.832-1.024 | 0.132 |
| Child–Pugh score, <6 | 1.523 | 0.305-7.601 | 0.608 |
| EHS, absence | 1.078 | 0.182-6.384 | 0.934 |
| AFP, <90 ng/mL | 3.061 | 0.564-16.598 | 0.195 |
| PIVKA-II, <540 mAU/mL | 2.963 | 0.686-12.794 | 0.146 |
| 8W-RDI, per 1% increment | 1.036 | 1.001-1.072 | **0.041** |

AFP: Alpha-fetoprotein; CI: confidence interval; EHS: extrahepatic spread; PIVKA-II: protein induced by vitamin K absence or antagonist-II. †Estimated using logistic regression analysis. Bold font indicates significant *p*-values.

## Results

*Patient characteristics*. The clinical profiles of the 50 study patients are summarized in Table I. Eleven deaths occurred during the observational period. The median follow-up period was 6.6 months; PFS was 5.8 months, time to treatment failure was 4.4 months, and median OS was not reached. The best overall response was PR in 22 patients (responders; no patient had CR) and SD and PD in 14 patients each, respectively (non-responders), giving an overall response rate of 44% and a disease control rate of 72%. Among responders, 21 out of 22 patients (95.5%) demonstrated PR at first evaluation after starting lenvatinib, and the median time to response was 7.8 weeks.

*Factors associated with OR*. Univariate analysis indicated that the median 8W-RDI in responders was significantly higher than that in non-responders ($p<0.001$; Table I). Age, Child–Pugh score, EHS, AFP, PIVKA-II, and 8W-RDI were entered into multivariate analysis. Multivariate logistic regression analyses revealed that 8W-RDI was the only independent factor predictive of response (odds ratio=1.036, 95% CI=1.001-1.072; $p=0.041$; Table II).

*Optimal cut-off value of RDI*. An 8W-RDI of 75% was determined to be the optimal cut-off value differentiating responders from non-responders, with a sensitivity of 72.7% and specificity of 71.4% by ROC curve (Figure 1). Among 25 (50%) patients classified as having 8W-RDI ≥75%, their

best overall responses were PR, SD and PD in 68%, 24% and 8%, respectively, while among 25 (50%) patients classified as having 8W-RDI <75%, best responses were 20%, 32% and 48%, respectively, (Figure 2A). Furthermore, PFS was significantly longer in patients with 8W-RDI of ≥75% compared to those with 8W-RDI <75% [median PFS=7.4 (95% CI=5.9-9.8) *vs*. 3.3 (95% CI=1.4-5.8) months, respectively; $p$=0.004] (Figure 2B). The clinical characteristics of patients in whom 8W-RDI ≥75% was maintained are shown in Table III. Patients with 8W-RDI ≥75% were more likely to have a Child–Pugh score of 5, ALBI grade of 1, and presence of EHS by univariate analysis. All patients who started with a reduced dose were classified into the low 8W-RDI group.

*AEs and DLTs*. In this study, 42 (84%) patients experienced DLTs: Drug interruption in 30 (60%), dose reduction in 34 (68%), and treatment withdrawal in nine (18%) owing to intolerable side-effects. Thirty-two (64%) patients developed DLTs during the first 8 weeks of treatment, and treatment withdrawal during the first 8 weeks caused by AEs was necessary in six (12%) patients. Table IV shows incidence of individual AEs and AEs that caused DLTs during the initial 8 weeks. Regarding DLTs during the initial 8 weeks, fatigue was the most common reason (n=12, 24%), followed by appetite loss (n=5, 10%), reduced platelet count (n=5, 10%) and proteinuria (n=5, 10%); hypertension and hypothyroidism were uncommon among DLTs, despite their high frequency.

## Discussion

Several prospective randomized trials on HCC (7-10) have demonstrated a significant correlation between OR evaluated by mRECIST and good prognosis. Thus, the importance of OR as a candidate surrogate endpoint of OS has been recognized (8, 23). Since no clear parameters exist for predicting the OR to lenvatinib therapy, the identification of such clinical parameters has become increasingly crucial. The present results demonstrated that 8W-RDI to be the only significant factor affecting OR in multivariate analysis (odds ratio=1.036, 95% CI=1.001-1.072; $p$=0.041), independent of standard clinical features. As far as we are aware, this is the first report to clarify the impact of RDI on treatment response in patients with HCC treated with lenvatinib.

In this retrospective study, 22 (44%) patients achieved OR in the follow-up period. Among responders, 21 out of 22 patients (95.5%) achieved OR at first evaluation after beginning lenvatinib therapy, and the other patient achieved OR at 24 weeks. The median time to response was 7.8 weeks, and the patient who achieved OR at 24 weeks had an 8W-RDI of 93%. Thus, the definition of 8W-RDI as an early-phase indicator of the doses required for OR appears to be reasonable.

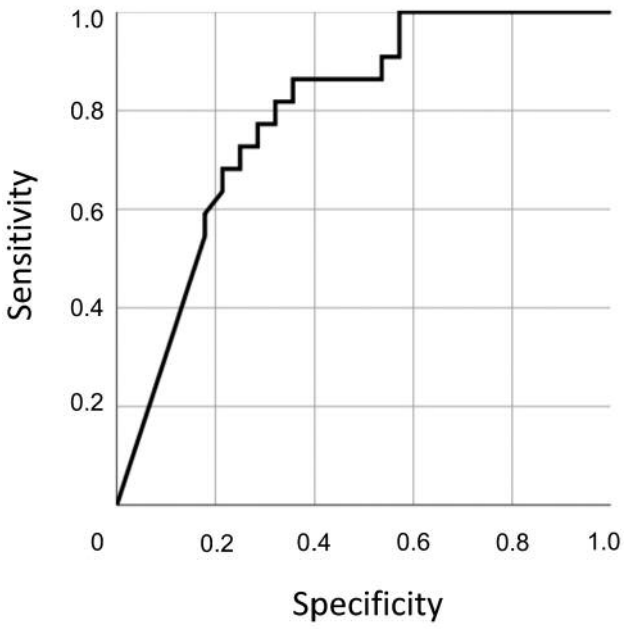


Figure 1. *Receiver operating curves of the relative lenvatinib dose intensity 8 weeks after induction associated with objective response in patients with hepatocellular carcinoma treated with lenvatinib.*

An 8W-RDI of 75% was determined to be the optimal cut-off value for differentiating responders from non-responders. At this cut-off value, the sensitivity and specificity were 72.7% and 71.4%, respectively. The response rate in 25 (50%) patients with 8W-RDI ≥75% was greater (68% *vs*. 20%) and the PFS longer (7.4 *vs*. 3.3 months) compared with patients with 8W-RDI <75%. For other cancer types treated with TKIs, RDI cut-off values ranging from 60% to 80% during the initial 3-12 weeks have been reported as predictive of longer PFS and OS (14-17). Our data concur with those cut-off values.

Our results suggest that lenvatinib may have dose-dependent antitumor effects on HCC. A high RDI may have contributed to response because patients treated with a high RDI have a higher plasma concentration of lenvatinib than patients with low RDI. Hayato *et al*. reported that according to a pharmacokinetic/pharmacodynamic analysis, high relative doses of lenvatinib in simulations provided favorable clinical efficacy in patients with thyroid cancer (24). Additionally, several studies have revealed a correlation between higher plasma tyrosine kinase inhibitor concentration and better clinical outcomes in other types of cancer (25, 26). To our knowledge, this is the first report to identify an association between the actual dose delivered and treatment efficacy in patients with HCC treated with TKIs.

AE management is considered to be important for maintaining dose intensity. In the present study, fatigue was

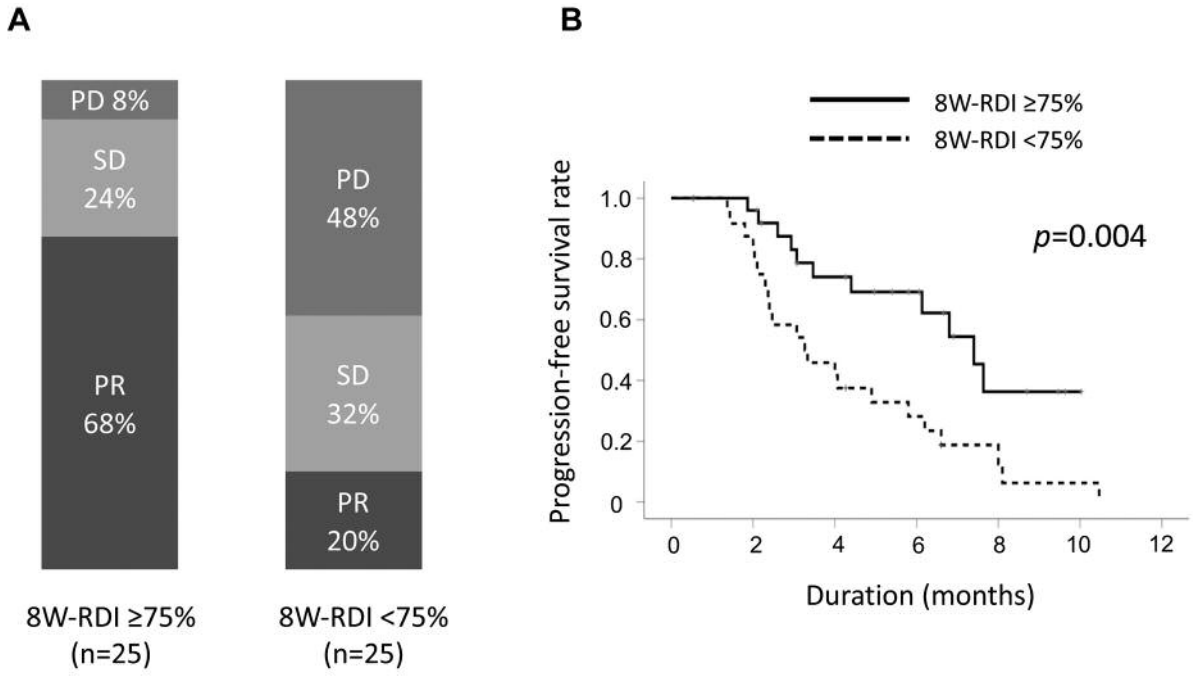


Figure 2. *A: Frequency of best overall response to lenvatinib in patients with hepatocellular carcinoma according to relative lenvatinib dose intensity 8 weeks after induction (8W-RDI) threshold. B: Cumulative progression-free survival rate according to 8W-RDI threshold. PD: Progressive disease; SD: stable disease; PR: partial response.*

Table III. *Patient characteristics according to relative dose intensity 8 weeks after lenvatinib induction*[†].

| Variable | | 8W-RDI | | *p*-Value |
|---|---|---|---|---|
| | | ≥75% | <75% | |
| Age, years | Median (range) | 70 (53-89) | 79 (57-93) | 0.095 |
| Sex, n | Male/female | 22/3 | 16/9 | 0.095 |
| ECOG-PS, n | 0/≥1 | 18/7 | 19/6 | 1.000 |
| Body weight, n | <60/≥60 kg | 19/6 | 14/11 | 0.232 |
| Viral infection, n | Yes/no | 15/10 | 12/13 | 0.571 |
| Child–Pugh score, n | 5/≥6 | 21/4 | 9/16 | **0.001** |
| ALBI, n | 1/2 | 14/11 | 4/21 | **0.007** |
| EHS, n | Yes/no | 11/14 | 2/23 | **0.008** |
| MVI, n | Yes/no | 3/22 | 5/20 | 0.463 |
| AFP, n | <90/≥90 ng/ml | 16/9 | 11/14 | 0.256 |
| PIVKA-II, n | <540/≥540 mAU/ml | 14/11 | 12/13 | 0.778 |
| Initial dose of LEN, n | Full/reduced | 25/0 | 20/5 | **0.022** |

ECOG: Eastern Cooperative Oncology Group; PS: performance status; HBV: hepatitis B virus; HCV: hepatitis C virus; ALBI: albumin-bilirubin; EHS: extrahepatic spread; MVI: macrovascular invasion; AFP: alpha-fetoprotein; PIVKA-II: protein induced by vitamin K absence or antagonist-II; TACE: transarterial chemoembolization; LEN: lenvatinib; 8W-RDI: relative dose intensity 8 weeks after lenvatinib induction. Bold font indicates significant *p*-values.

by far the most common DLT during the first 8 weeks, followed by appetite loss, reduced platelet count, and proteinuria. Prophylactic use of dexamethasone has been proposed to be effective in reducing fatigue during regorafenib treatment in patients with metastatic colorectal cancer, thereby prolonging the time to regorafenib dose modification (27, 28). The beneficial effects of the herbal drug *Bojungikki-tang* (Chinese; *Hochu-ekki-to* in Japanese)

Table IV. *Adverse events (AEs) and dose-limiting toxicities (DLTs) during the initial 8 weeks of lenvatinib therapy in patients with hepatocellular carcinoma.*

| Adverse event | Total* | DLTs during initial 8 weeks, n (%) | |
|---|---|---|---|
| | | 8W-RDI ≥75% | 8W-RDI <75% |
| Fatigue | 25 (50%) | 3 (6%) | 9 (18%) |
| Hypertension | 36 (72%) | 0 | 1 (2%) |
| Diarrhea | 10 (20%) | 0 | 3 (6%) |
| Appetite loss | 13 (26%) | 1 (2%) | 4 (8%) |
| Nausea | 6 (12%) | 0 | 3 (6%) |
| Hand-foot skin reaction | 26 (52%) | 2 (4%) | 1 (2%) |
| Decreased platelets | 8 (16%) | 1 (2%) | 4 (8%) |
| Proteinuria | 25 (50%) | 2 (4%) | 3 (6%) |
| Hypothyroidism | 30 (60%) | 0 | 0 |
| Decreased liver function | 11 (22%) | 1 (2%) | 2 (4%) |
| Hepatic encephalopathy | 4 (8%) | 0 | 3 (6%) |
| Rupture of esophageal varices | 2 (4%) | 0 | 2 (4%) |

*Evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0 (21).

in the management of cancer-related fatigue have also been reported (29). In order to clarify whether such supportive care might help maintain a high RDI for patients with HCC, further prospective studies are needed.

The 8W-RDI was also affected by the characteristics of patients before treatment. The present results revealed a Child–Pugh score of 5, ALBI grade of 1, and presence of EHS as significant factors in univariate analysis for high 8W-RDI. The relationship between Child–Pugh score of 5/6 or ALBI grade of 1/2 and dose modification due to lenvatinib-induced toxicity has not been clarified. However, it has been reported that DLTs are more likely to occur in patients with HCC with Child–Pugh score of B than those with a score of A (30). Since lenvatinib is primarily metabolized by cytochrome P450 3A4 (31), hepatic dysfunction may lead to increased lenvatinib exposure (32) and a consequent decrease in RDI. The impact of reduced liver function also explains why it was possible to maintain a high RDI in patients with EHS. The ALBI grade of patients with EHS was significantly better than that of those without ($p$=0.03) (data not shown). Further studies are required to determine the association between RDI and liver function and HCC profile in patients treated with lenvatinib.

This study has several limitations. It was a retrospective multi-center study with a small patient cohort. The findings were affected by unavoidable biases in patient selection. Since we were unable to investigate the associations between 8W-RDI and OS due to the short follow-up period, whether the 8W-RDI of lenvatinib affects long-term disease control in patients with HCC remains unclear. Further studies to validate the present data in a large cohort and identify pre-treatment risk factors for reduced RDI are needed.

In conclusion, we have identified a clear goal during early-phase treatment of HCC with lenvatinib. The present results suggest that maintaining a high dose intensity of lenvatinib during at least the initial 8 weeks of treatment may enable better responses among patients with HCC. This evidence-based therapeutic target will not only help clinicians select the most appropriate therapy from among several options, but also encourage both clinicians and patients to maintain their motivation in favor of HCC treatment.

## Conflicts of Interest

Yoshito Itoh received lecture fees from the Bristol-Myers Squibb Company and Merck Sharp and Dohme and commercial research funding from Bayer AG, Eisai Co., Ltd., Bristol-Myers Squibb Company, and Merck Sharp and Dohme. Michihisa Moriguchi received lecture fees from Bayer AG and Eisai Co., Ltd.

## Authors' Contributions

Conception and design: A.T., M.M., Y.S. Provision of study materials or patients: A.T., M.M., Y.S., H.I., T.Y., H.K., H.F., T.S., Y.M., H.I, H.T., Y.N., M.J., M.A., T.H., A.O., A.M., A.M., N.Y., T.N., H.M., A.U., T.N., K.Y., Y.I. Collection and assembly of data: A.T., M.M., Y.S. Data analysis and interpretation: all Authors. Article writing: all Authors. Final approval of article: all Authors.

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