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Original Article

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Maximum Plasma Concentration of Lenvatinib Is Useful for Predicting Thrombocytopenia in Patients Treated for Hepatocellular Carcinoma

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Abstract

Background: Although lenvatinib treatment has a favorable efficacy for unresectable hepatocellular carcinoma (HCC), it is associated with adverse events (AEs) that must be closely monitored and managed. Thrombocytopenia is one of the major AEs. The aim of this study was to clarify whether thrombocytopenia can be predicted by the plasma concentration of lenvatinib.

Methods: This was a single-center retrospective observational study. Twenty-three patients with unresectable HCC and pharmacokinetics data at the initial lenvatinib administration between May 2018 and September 2020 at Oita University Hospital were enrolled. The AEs during the 4 weeks after the initiation of treatment were evaluated, and the correlations between the thrombocytopenia and the plasma concentration of lenvatinib were examined. Spearman's correlation was used to evaluate the correlation between two continuous variables.

Results: The rate of platelet count decrease correlated with the maximum plasma concentration (C_{max}) (r = 0.65, P = 0.001), whereas it did not with the minimum plasma concentration (C_{min}) (r = 0.29, P = 0.206). After stepwise multiple linear regression analysis, the starting dose of lenvatinib and the serum albumin concentration were identified as independent explanatory variables. Next, a formula for predicting the C_{max} using these two variables was created. The predicted C_{max} was strongly correlated with the C_{max} (r = 0.87, P < 0.0001) and the rate of platelet count decrease (r = 0.67, P = 0.001).

Conclusions: This study identified the usefulness of the drug C_{max} to predict the rate of platelet count decrease within 4 weeks after the initiation of treatment. Although it is difficult to measure the plasma concentration of lenvatinib in community hospitals, the predicted C_{max} is useful for predicting the rate of platelet count decrease with this treatment.

Keywords: Hepatocellular carcinoma; Lenvatinib; Plasma concentration; Thrombocytopenia

Introduction

Hepatocellular carcinoma (HCC) is one of the most frequently occurring cancers worldwide [1]. If HCC is detected at an early stage and radical treatment is given, the prognosis is not poor [2]. However, HCCs often develop into advanced-stage tumors due to the peculiar features of HCC such as multicentric occurrence and intrahepatic metastasis [3, 4], even if repeated radical treatments are performed. Moreover, hepatitis virus-unrelated (non-B non-C) HCC, which is currently increasing in Japan [5], is often found at the advanced stage [6]. Although transcatheter arterial chemoembolization (TACE) has been widely performed for unresectable HCC [7], repeated TACE results in deterioration of hepatic function, which prevents the introduction of a molecular-targeted drug [8]. Sorafenib has been established as a standard therapy for unresectable advanced HCC since 2007, and it prolonged the overall survival of patients by about 3 months compared to a placebo in the SHARP study [9]. Recently, lenvatinib has become popular as a systemic chemotherapeutic drug for HCC [10]. This drug is a multitargeted tyrosine kinase inhibitor of the vascular endothelial growth factor receptor (VEGFR) family, fibroblast growth factor receptor family, platelet-derived growth factor receptor-alpha, rearranged during transfection, and KIT [11, 12]. The phase 3 REFLECT trial demonstrated that patients treated with lenvatinib had a similar overall survival as those treated with sorafenib, but the progression-free survival, time to progression, and overall response rate of those treated with lenvatinib were significantly greater than those treated by sorafenib [10]. Lenvatinib is a drug that was developed as a treatment for thyroid cancer at a daily dose of 24 mg [13]. Because many patients with HCC have impaired liver function, phase 1 and phase 2 studies for lenvatinib in HCC patients were conducted at a daily dose of 12 mg [14, 15]. A population pharmacokinetic and exposure-

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response analysis has revealed associations between early drug withdrawal or dose reduction and the area under the curve of the lenvatinib plasma concentration as well as body weight [16]. Based on these findings, a phase 3 study was conducted showing that the optimal dose is 8 mg for a body weight of less than 60 kg and 12 mg for a body weight of 60 kg or more [10]. In this setting, if adverse events (AEs) can be predicted by the lenvatinib plasma concentration, the risk of AEs due to lenvatinib therapy can be reduced in advance, thus avoiding withdrawal of treatment and allowing long-term continuation of treatment. Therefore, the purpose of this study was to clarify whether thrombocytopenia, which is a major AE in HCC patients treated with lenvatinib, can be predicted by measuring the lenvatinib plasma concentration.

Materials and Methods

Patients

This was a single-center retrospective observational study that was conducted with the approval of the Ethics Board of our hospital (approval number: 1476 for lenvatinib pharmacokinetics analysis, 1655 for the observational study) and was performed in accordance with the Declaration of Helsinki. A total of 30 consecutive patients starting lenvatinib (Eisai Co., Ltd, Tokyo, Japan) treatment for HCC between May 2018 and September 2020 at our hospital were enrolled in this study. The inclusion criteria for this study were as follows: patients with intermediate-stage or advanced-stage HCC according to the Barcelona Clinic Liver Cancer staging classification [17], patients with HCC that was not applicable to surgical resection or radiofrequency ablation therapy, patients with HCC that was not eligible for TACE or was refractory to TACE, and patients with Child-Pugh (CP) class A or B. All 30 patients matched these criteria. Pharmacokinetics analysis at the time of the initial administration of lenvatinib was started with the fifth patient among the 30 consecutive patients. Overall, three patients refused to have pharmacokinetics analysis performed. Finally, a total of 23 patients whose drug plasma concentration was measured were included in this study.

Blood sampling

The patients weighing < 60 kg received lenvatinib orally at an initial dose of 8 mg/day, while the patients weighing ≥ 60 kg received lenvatinib orally at an initial dose of 12 mg/day; however, if the attending physician decided that a dose reduction was necessary considering the patient's conditions such as age or liver function, the initial dose was reduced. After starting lenvatinib treatment, the attending physician could also modify the dose considering the patient's condition. Pharmacokinetics analysis was performed at the first drug administration, and the blood was sampled before taking lenvatinib as well as 1, 2, 4, 8, and 24 h after taking the drug. After the measurements of five patients were completed, the protocol was changed. Another 18 patients were analyzed by the following modified pharmacokinetics protocol: blood was sampled before taking lenvatinib as well as 2, 4, 6, 8, 12, and 24 h after taking the drug. The maximum plasma concentration observed (C_{max}), the minimum plasma concentration observed (C_{min}), that is, the plasma concentration after 24 h, and the time that the maximum plasma concentration (T_{max}) was reached were determined by the pharmacokinetics analysis. Blood samples were collected from the patient's brachial vein into a blood collection tube containing EDTA-2Na and were immediately centrifuged at 3,500 rpm and 25 °C for 5 min. Plasma samples were stored frozen at -40 °C until use. Quantification of lenvatinib was performed using ultra-performance liquid chromatography coupled to tandem mass spectrometry (UPLC-MS/MS) [18].

Measurement of lenvatinib using UPLC-MS/MS

The plasma concentration of lenvatinib was measured using UPLC-MS/MS [18]. Calibration, quality control (QC), and internal standard (IS) solutions were prepared by diluting the stock solution in 100% methanol. Deuterated lenvatinib (lenvatinib-d_4) was used as an IS. For sample pretreatment, solid-phase extraction with an OASIS® MCX μElution plate was used. For the calibration or QC sample, 330 μL of 4% aqueous phosphoric acid solution, 20 μL of IS (100 ng/mL), 100 μL of calibration or QC solution, and 100 μL of blank plasma were added to a 2-mL polypropylene tube and vortexed for 20 s. The patient plasma sample (100 μL) was mixed with 330 μL of 4% aqueous phosphoric acid solution, 20 μL of IS (100 ng/mL), and 100 μL of 100% methanol for volume adjustment. The MCX μElution plate was conditioned and equilibrated by adding 200 μL of 100% methanol and 200 μL of ultrapure water to each well. Then, 500 μL of the above mixture containing calibration, QC, or patient sample was added to each well. Each well was washed with 200 μL of 2% aqueous formic acid solution followed by 200 μL of 100% methanol. After the washing step, the analyte was eluted with 100 μL of 1.25% ammonium solution (25% aqueous ammonia/100% methanol = 5/95) into a round-well collection plate (Waters). Subsequently, 100 μL of ultrapure water was added to each well, and the contents were mixed by pipetting. The plate was sealed with an adhesive seal (Waters). The injection volume was 10 μL. Lenvatinib was separated using an ACQUITY UPLC® BEH C18 column. The MS/MS transitions monitored in the positive ionization mode for lenvatinib and lenvatinib-d_4 were *m/z* 427.02 → *m/z* 370.05 and *m/z* 431.09 → *m/z* 370.05, respectively. The mobile phase was a gradient of 0.1% aqueous formic acid solution:0.1% formic acid/acetonitrile solution. Validation was performed according to the US Food and Drug Administration guidelines.

Correlation between platelet count decrease and lenvatinib plasma concentration

The AEs during the 4 weeks (28 days) after the initiation of lenvatinib treatment were evaluated by Common Terminology Criteria for AEs (CTCAE), version 5.0. In addition, the number of patients with interruption or dose reduction of lenvatinib as well as the causes of interruption or reduction was evaluated. The total lenvatinib dose for 4 weeks was assessed, exclud-

Table 1. Baseline Characteristics of Patients (n = 23)

Characteristic	Number or median (range)
Age (years)	77 (56 - 93)
Sex (male/female)	19/4
Body weight (< 60 kg/≥ 60 kg)	11/12
Total bilirubin (mg/dL)	0.96 (0.4 - 1.9)
Albumin (g/dL)	3.5 (2.6 - 4.3)
White blood cell count (/μL)	5,070 (2,630 - 8,070)
Platelet count (10^4/μL)	11.1 (5.4 - 23.4)
Prothrombin time (%)	86.5 (51.5 - 14.8)
ALBI score	-2.13 (-3.03 to -1.35)
Child-Pugh class (A/B/C)	15/8/0
BCLC stage (B/C)	11/12
Starting dose of lenvatinib (4 mg/8 mg/12 mg)	10/8/5

ALBI: albumin-bilirubin; BCLC: Barcelona Clinic Liver Cancer.

ing the patients who discontinued treatment. Since a platelet count decrease is an important AE that is often experienced by patients with HCC who are treated with lenvatinib, the rate of platelet count decrease ((pretreatment value - minimum value for 4 weeks)/pretreatment value × 100 (%)) was calculated. The correlations between the rate of platelet count decrease and the lenvatinib plasma concentration, baseline characteristics of the patients, and the total lenvatinib dose for 4 weeks were analyzed; two patients who discontinued treatment (one patient discontinued treatment at day 4 and one patient discontinued treatment at day 5) were excluded from this analysis.

Furthermore, since it is difficult to measure the lenvatinib plasma concentration in community hospitals, a formula for predicting the C_{max} was created. The prediction formula was created using data from all patients (n = 23), including the two patients who discontinued treatment.

Statistical analysis

Continuous data were shown as the median and range or mean ± standard deviation. Independent continuous data were compared using the unpaired *t*-test. Spearman's correlation was used to evaluate the correlation between two continuous variables. Stepwise multiple linear regression analysis was performed to create a formula for predicting the C_{max}. A P-value less than 0.05 was considered statistically significant. All statistical analyses were performed using the software IBM SPSS Statistics version 22.0 for Windows.

Results

Baseline data and AEs within 4 weeks of treatment initiation

The baseline characteristics of the 23 patients included in this study before treatment with lenvatinib are summarized in Table 1. The AEs within 4 weeks of treatment initiation of any grade are listed in Table 2. A platelet count decrease was the most frequently found AE, with worsened CTCAE grade observed in 52.2% (12/23) of the patients (Fig. 1). Among the 23 patients, two patients discontinued the treatment, including one patient who discontinued treatment at day 4 due to hemobilia and one patient who discontinued treatment at day 5 due to an increase in the creatinine level. A dose reduction was needed in 10 patients due to a platelet count decrease (n = 5), anorexia plus malaise (n = 2), anorexia plus encephalopathy (n = 1), colitis (n = 1), or a suspected urinary tract infection (n = 1). Drug interruption was required for two patients due to anorexia plus hepatic encephalopathy (n = 1) or anorexia (n = 1). Although four patients had a dose increase (4 - 8 mg for two patients and 8 - 12 mg for two patients),

Table 2. Adverse Events Within 4 Weeks of Lenvatinib Initiation in All Patients (n = 23)

Adverse event	n (%)
Platelet count decrease	12 (52.2%)
Hypertension	11 (47.8%)
Anorexia	11 (47.8%)
Malaise	9 (39.1%)
Diarrhea	8 (34.8%)
Hypothyroidism	6 (26.1%)
White blood cell count decrease	5 (21.7%)
Palmar-plantar erythrodysesthesia syndrome	3 (13.0%)
Hoarseness	3 (13.0%)
Encephalopathy	2 (8.7%)
Hemobilia	1 (4.3%)
Colitis	1 (4.3%)
Creatine increase	1 (4.3%)

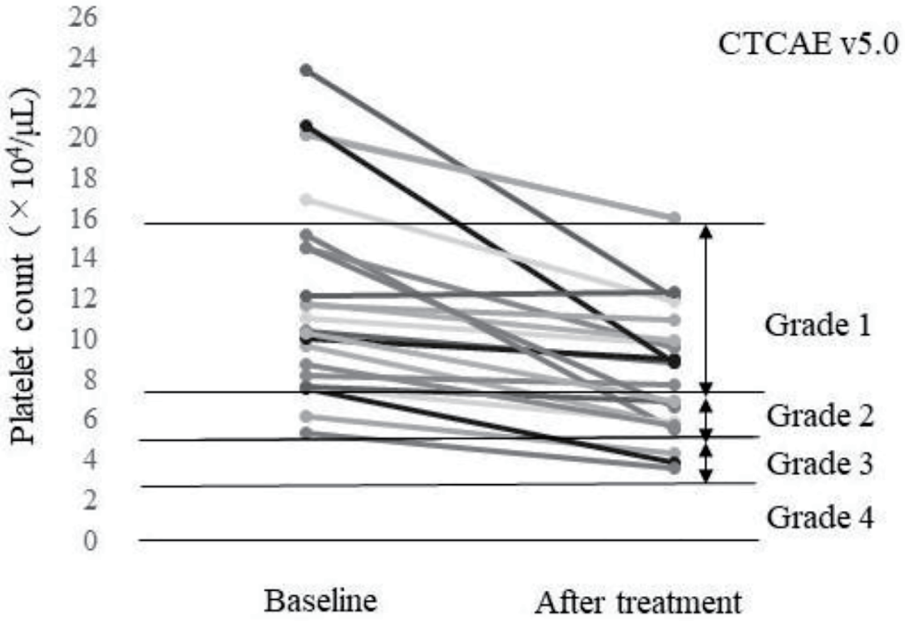

Figure 1. Platelet count of each patient at baseline and after treatment (n = 23). A total of 52.2% (12/23) of the patients had a worsened platelet count grade according to the Common Terminology Criteria for AEs v5.0 (CTCAE v5.0).

three of these patients returned to the starting dose due to AEs.

Lenvatinib pharmacokinetics

For the patients with a starting dose of 4 mg (n = 10), the mean C_{max} was 43.7 ± 21.3 ng/mL, the mean C_{min} was 11.4 ± 3.9 ng/mL, and the T_{max} values were 4 h for six patients, 6 h for one patient, 8 h for two patients, and 12 h for one patient. For the patients with a starting dose of 8 mg (n = 8), the mean C_{max} was 68.3 ± 18.1 ng/mL, the mean C_{min} was 18.5 ± 4.8 ng/mL, and the T_{max} values were 4 h for one patient, 6 h for one patient, and 8 h for six patients. For the patients with a starting dose of 12 mg (n = 5), the mean C_{max} was 134.2 ± 24.9 ng/mL, the mean C_{min} was 21.6 ± 6.9 ng/mL, and the T_{max} values were 4 h for three patients, 6 h for one patient, and 8 h for one patient.

Correlation between rate of platelet count decrease and lenvatinib plasma concentration

Figure 2 shows the correlations between the rate of platelet count decrease and the C_{max}, C_{min}, starting dose, and total dose within 4 weeks of treatment initiation (n = 21). There were correlations between the rate of platelet count decrease and the C_{max} (r = 0.65, P = 0.001), starting dose (r = 0.63, P = 0.002), and total dose within 4 weeks (r = 0.62, P = 0.003). No significant correlation was found between the rate of platelet count decrease and the C_{min} (r = 0.29, P = 0.206). The correlations between the rate of platelet count decrease and the C_{max} as well as the starting dose were analyzed in patients with (n = 15) or without (n = 6) dose modifications (Fig. 3). A significant correlation was found between the rate of platelet count decrease and the C_{max} (r = 0.84, P = 0.037) in patients without dose modifications within 4 weeks of treatment initiation (n = 6). Significant correlations were also found between the rate of platelet count decrease and the C_{max} (r = 0.64, P = 0.011) as well as the starting dose (r = 0.65, P = 0.008) in patients with dose modifications within 4 weeks of treatment initiation (n = 15).

Creation of a C_{max} prediction formula

The analysis to create a C_{max} prediction formula that included patients who discontinued treatment (n = 23) was performed. The C_{max} was strongly correlated with the starting dose of lenvatinib (r = 0.84, P < 0.0001). Stepwise multiple linear regression analysis was performed to create a formula for predicting the C_{max} using the baseline characteristics (Table 1) as explanatory variables, excluding the body weight as it is closely related to the starting dose. The results demonstrated that the starting dose and the serum albumin value concentration were independent explanatory variables (Table 3). Therefore, the prediction formula was as follows: predicted C_{max} (ng/mL) = (starting dose (mg) × 10.177) + (serum albumin value (g/dL) × 23.219) - 80.769. The predicted C_{max} was strongly correlated with the C_{max} (r = 0.87, P < 0.0001) for all patients (n = 23) as well as with the rate of platelet count decrease (r = 0.67, P = 0.001) for the patients without drug withdrawal (n = 21) (Fig. 4a, b). For the six patients without dose modifications, the rate of platelet count decrease tended to increase in the patients with a high predicted C_{max} (r = 0.80, P = 0.053). For the 15 patients with dose modifications, the rate of platelet count decrease and the predicted C_{max} were significantly correlated (r =

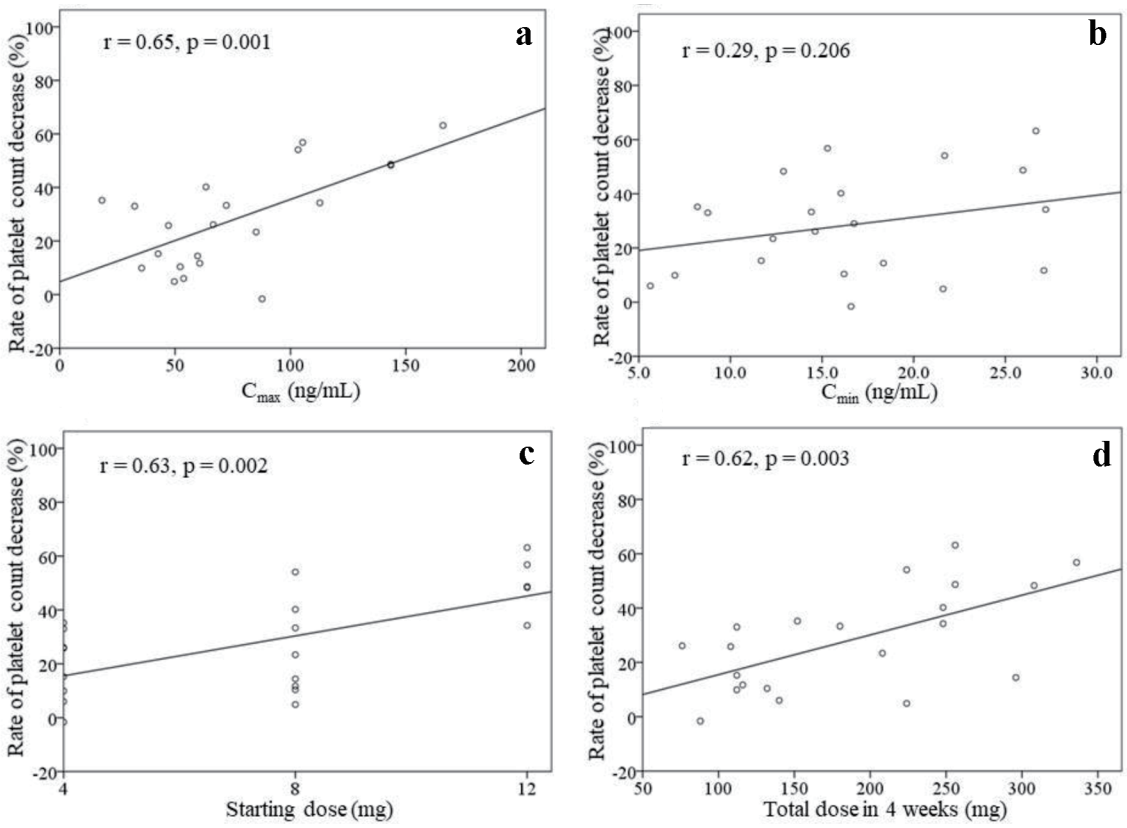

Figure 2. Rate of platelet count decrease, excluding two patients with drug withdrawal (n = 21). The correlations between the rate of platelet count decrease and the C_{max} (a), C_{min} (b), starting dose (c), and total dose of lenvatinib within 4 weeks of treatment initiation (d) are shown.

0.63, P = 0.012) (Fig. 4c, d).

Comparison of the patients with an albumin concentration < 3.5 g/dL (n = 11) and the patients with an albumin concentration ≥ 3.5 g/dL (n = 12) demonstrated that the T_{max} was significantly longer in the group with an albumin concentration < 3.5 g/dL than in the group with an albumin concentration ≥ 3.5 g/dL group (T_{max}: 7.5 ± 2.2 h vs. 5.0 ± 1.6 h, P = 0.006).

Discussion

Thrombocytopenia is a common side effect of lenvatinib treatment [10, 14, 15]. In a phase 3 study of lenvatinib (daily dose of 24 mg) for the treatment of radioiodine-refractory differentiated thyroid cancer, the incidence of thrombocytopenia was reported to be 8.8% (1.5%: grade ≥ 3) overall in the SELECT trial [13, 19] and 46.7% (grade ≥ 3: 6.7%) in Japanese patients [19]. In a phase 2 study of lenvatinib at a daily dose of 12 mg for advanced HCC, thrombocytopenia was observed in 34.8% of patients (grade ≥ 3: 21.8%) [15]. Meanwhile, in a randomized phase 3 trial (12 mg/day for a body weight ≥ 60 kg or 8 mg/day for a body weight < 60 kg), the incidence of thrombocytopenia was reported to be 18% (grade ≥ 3: 5%) in the lenvatinib group [10]. In our study, thrombocytopenia was the most frequently found AE, occurring in 52.2% (12/23) of the patients, and a dose reduction was needed in 21.7% (5/23) of the patients.

Our study revealed that the C_{max} at the initial administration of lenvatinib was correlated with the rate of platelet count decrease within 4 weeks. The starting dose also was correlated with the rate of platelet count decrease because it was closely related to the C_{max}. A previous dose-escalation study of lenvatinib has reported that the C_{max} at the first administration and the C_{max} at steady state were dose proportional [20]. In our study, among several variables, the C_{max} at the first administration of lenvatinib was the most correlated with the rate of platelet count decrease. Since many patients had a dose change within 4 weeks of initiation of treatment, the total lenvatinib dose within the first 4 weeks of treatment was included in these variables. Furthermore, the C_{max} also was correlated with the rate of platelet count decrease, even in patients with dose modifications.

This study identified the usefulness of the plasma lenvatinib concentration measurement to predict the platelet count decrease. However, since it is difficult to measure the plasma lenvatinib concentration in community hospitals, we created a prediction formula for C_{max} using multiple regression analysis. This prediction formula consists of the starting dose of lenvatinib and the serum albumin concentration. In this study, the T_{max} of lenvatinib in the group with a serum albumin concentration < 3.5 g/dL was longer than that in the group with a serum albumin concentration ≥ 3.5 g/dL; thus, absorption

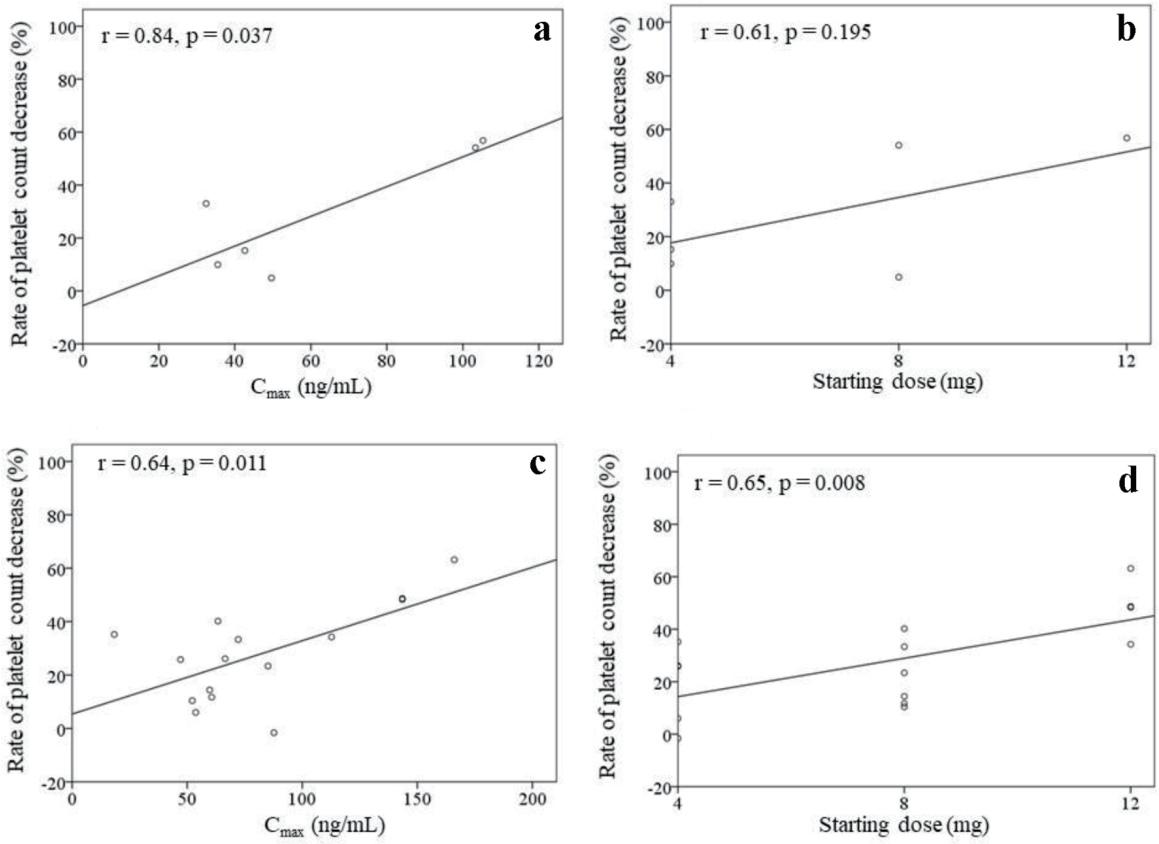

Figure 3. Rates of platelet count decrease in patients without dose modifications within 4 weeks (a, b) (n = 6) as well as in patients with dose modifications within 4 weeks (c, d) (n = 15) of lenvatinib initiation. The correlations between the rate of platelet count decrease and the C_{max} as well as the starting dose of lenvatinib are shown.

of lenvatinib by the intestinal tract may affect the C_{max}. Lenvatinib may have an increased tissue migration in low serum albumin conditions due to the high binding rate of lenvatinib to serum proteins (96.6-98.2% in patients with advanced solid tumors) [20]. This formula using the starting dose of lenvatinib and the serum albumin concentration was strongly correlated with the C_{max}; therefore, the predicted C_{max} was useful for predicting the rate of platelet count decrease.

VEGFs play important roles in megakaryocytic cell lines [21]. During the development from hematopoietic stem cells to megakaryocytes, VEGFR1, VEGFR2, and VEGFR3 are expressed at different developmental stages [21]. Lenvatinib-induced thrombocytopenia may be caused by its inhibitory effect on VEGFRs in platelet formation. Therefore, a dose reduction or drug interruption is considered to be effective for recovery of the platelet count. The usefulness of partial splenic embolization (PSE) for patients with thrombocytopenia treated with lenvatinib has been reported [22]. If the rate of platelet count decrease can be predicted before lenvatinib treatment, PSE is a useful strategy to avoid a dose reduction or drug interruption.

This study has some limitations that must be mentioned. First, the number of patients analyzed was small. In addition, this study included patients who needed dose modifications within 4 weeks of treatment initiation. Therefore, the results of this study may not be sufficient to be generalizable.

Conclusion

The C_{max} at the initial administration of lenvatinib correlated with the rate of platelet count decrease within 4 weeks. The

Table 3. Stepwise Multiple Linear Regression Analysis for Creating a C_{max} Prediction Formula

	β	SE	Standardized β	t	P-value
Constant	-80.769	33.788		-2.390	0.027
Starting dose (mg)	10.177	1.400	0.797	7.271	< 0.0001
Albumin (g/dL)	23.219	9.712	0.262	2.391	0.027

R = 0.88, P = 0.027. SE: standard error; C_{max}: maximum plasma concentration.

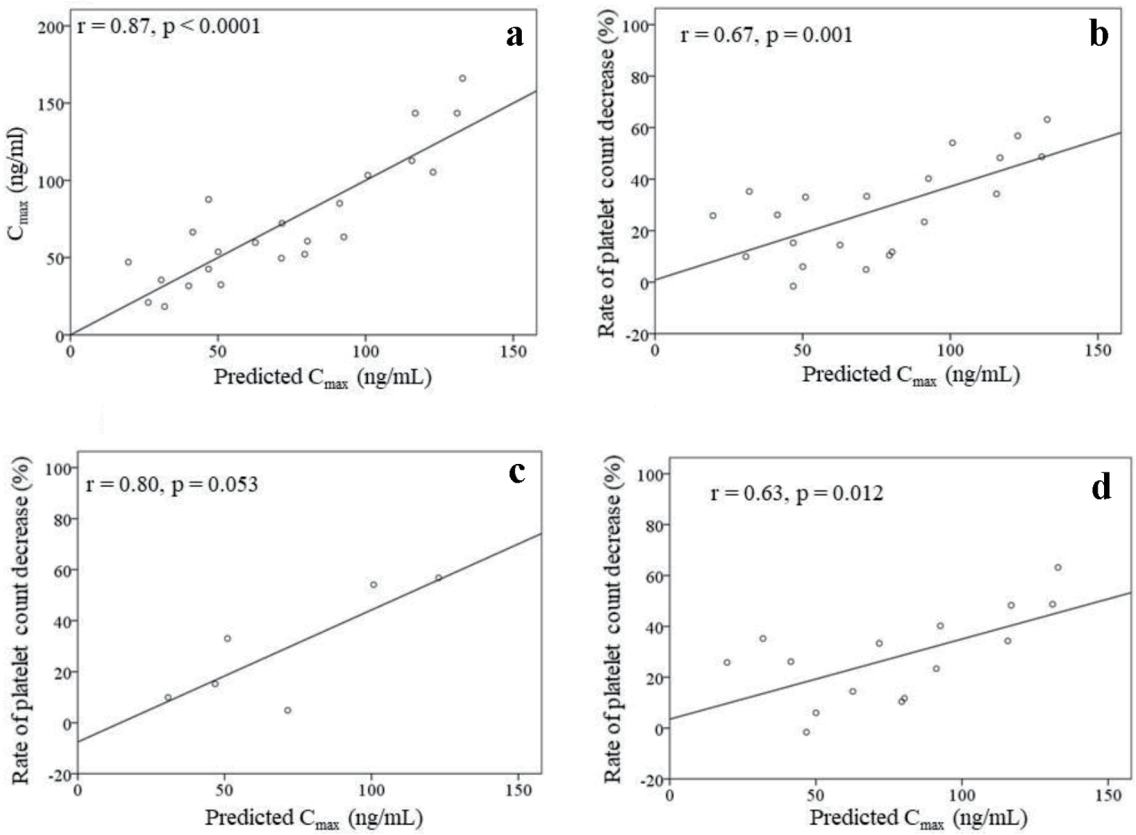

Figure 4. Correlation between the C_{max} and the predicted C_{max} (a) in all patients (n = 23). Correlations between the predicted C_{max} and the rate of platelet count decrease (b-d). (b) Patients without drug withdrawal within 4 weeks of lenvatinib initiation (n = 21). (c) Patients without dose modifications within 4 weeks of lenvatinib initiation (n = 6). (d) Patients with dose modifications within 4 weeks of lenvatinib initiation (n = 15).

predicted C_{max} is useful for predicting the rate of platelet count decrease in HCC patients treated with lenvatinib.

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Financial Disclosure

None to declare.

Conflict of Interest

We have no financial relationships to disclose.

Informed Consent

Before the pharmacokinetics analysis, written informed consent was obtained from all 23 patients.

Author Contributions

Endo M performed the research and wrote the paper; Honda K designed the research and supervised the report; Honda K, Shiraiwa K, Sueshige Y, Tanaka R, Tatsuta R and Itoh H acquired and analyzed the data; Endo M, Honda K, Tokumaru T, Saito T, Iwao M, Tokoro M, Arakawa M and Seike M performed the clinical work; Murakami K supervised the report; all authors approved the final version of the article.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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