Medical Oncology (2019) 36:39
https://doi.org/10.1007/s12032-019-1263-3

ORIGINAL PAPER

Association of lenvatinib trough plasma concentrations with lenvatinib-induced toxicities in Japanese patients with thyroid cancer

Mitsuji Nagahama[1] · Tomoko Ozeki[2] · Akifumi Suzuki[1] · Kiminori Sugino[1] · Takenori Niioka[2] · Koichi Ito[1] · Masatomo Miura[2]

Received: 23 January 2019 / Accepted: 18 March 2019 / Published online: 27 March 2019

Abstract

The aim of this study was to examine the association of lenvatinib-induced adverse events with the trough plasma concentration (C_0) in Japanese patients with thyroid cancer. Patients received lenvatinib 24 mg as an initial dose, and sequential dose reductions were conducted based on the grade of each side effect. Assessment of adverse events, assay of lenvatinib C_0, and analysis of clinical laboratory tests were performed at the same time of day and were retrospectively analyzed. There were no significant differences in lenvatinib C_0 among grades of hypertension, proteinuria, hand-foot syndrome, and diarrhea. However, levels of aspartate transaminase, alanine transaminase, and total bilirubin were significantly higher in lenvatinib C_0 quartile (Q) 4 ($\geq$ 88 ng/mL) than in Q1 (< 42 ng/mL) and Q2–3 (42–88 ng/mL). Additionally, platelet counts were highest in the lowest Q1 group. The median dose of lenvatinib in patients with *UGT1A1*6/*6* or **6/*28* (poor metabolizers [PMs]) was significantly lower than that in patients with *UGT1A1*1/*1* (10 and 14 mg, respectively), whereas the median bilirubin levels were significant higher in *UGT1A1* PMs (0.9 and 0.5 mg/dL, respectively). There were no significant differences in median lenvatinib C_0 values between patients with *UGT1A1*1/*1* and PMs (58.0 and 50.0 ng/mL, respectively). The threshold between the C_0 and toxicity of lenvatinib may be more than 88 ng/mL. Therefore, the dose of lenvatinib could be controlled to maintain a lower C_0 of less than 88 ng/mL. The target C_0 for lenvatinib as the threshold between the C_0 and optimal response may be in the range from 42 to 88 ng/mL; however, further studies are necessary.

Keywords Lenvatinib · *UGT1A1* · Polymorphism · Plasma concentration · Adverse events

Introduction

Lenvatinib, an oral multikinase inhibitor (KI) for vascular endothelial growth factor (VEGF) receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, stem cell factor receptor, and rearranged during transfection [1–4], is approved for the treatment of thyroid cancer. Hypertension is a known side effect of drugs that target the VEGF pathway [5], and lenvatinib-induced hypertension was found to occur in approximately 68% of patients in phase III clinical studies of lenvatinib treatment for radioiodine-refractory differentiated thyroid cancer [6]. Consequently, adverse events, such as hypertension, proteinuria, and diarrhea, necessitate dose reduction or dose interruption in patients receiving lenvatinib [6]. After administration of an initial daily dose of 24 mg lenvatinib, patients are subjected to dose reduction or dose interruption (63.9–73.6% and 79.4–86.8% of cases, respectively) [6].

Recently, a treatment strategy involving monitoring of plasma concentrations of KIs was introduced in the clinical setting. For many KIs, relationships between plasma concentrations and efficacy or toxicity have been reported [7]. For example, in sunitinib therapy, the sum of the total plasma trough concentration (C_0) of both sunitinib and its active metabolite *N*-desethyl sunitinib should be set above 50 ng/mL to obtain sufficient efficacy and below 100 ng/mL to avoid serious adverse events, such as thrombocytopenia [7]. However, no thresholds between the C_0 value and clinical efficacy or toxicity have been established for lenvatinib.

✉ Masatomo Miura
m-miura@hos.akita-u.ac.jp

[1] Department of Surgery, Ito Hospital, Tokyo, Japan

[2] Department of Pharmacy, Akita University Hospital, 1-1-1 Hondo, Akita 010-8543, Japan

In vitro, lenvatinib has been shown to inhibit human uridine diphosphate-glucuronosyltransferase (UGT) 1A1 activity for 17β-estradiol 3-glucuronidatin at a half-maximal inhibitory concentration of 10.6 μM [8]. In humans, glucuronidation of bilirubin by UGT1A1 results in the formation of bilirubin mono- and di-glucuronide, which are excreted into the bile [9, 10]. The genetic basis of the reduced bilirubin glucuronidation activity in Gilbert syndrome was revealed in 1995 [11]. All patients appeared to be homozygous for an additional TA in the TATAA box present in the proximal promoter of the *UGT1A1* gene ($[TA]_7TAA$ [named *UGT1A1*28*] compared with normal $[TA]_6TAA$). The presence of this TA insertion reduces the transcription of the gene to 20% of the normal value, resulting in a decrease in hepatic bilirubin glucuronidating activity by 80% in individuals with *UGT1A1*28/*28* [11]. Therefore, the *UGT1A1*28/*28* genotype is associated with unusually high bilirubin levels [11, 12]. In addition, *UGT1A1*6* (211G > A) isoforms have also been reported to cause a reduction in UGT1A1 enzyme activity [13]. Lenvatinib may inhibit the glucuronidation of bilirubin via UGT1A1, thereby increasing bilirubin levels. In particular, this inhibitory effect may be more pronounced in individuals who are poor metabolizers (PMs) of *UGT1A1*6/*6*, **6/*28*, and **28/*28*. However, it is still unclear whether patients who are *UGT1A1* PMs have an elevated risk of lenvatinib-induced hyperbilirubinemia.

Accordingly, in this study, we aimed to retrospectively examine the associations between lenvatinib-induced adverse events and trough plasma concentrations (C_0) in Japanese patients with thyroid cancer.

Methods

Patients and protocols

Fifty Japanese patients receiving treatment with lenvatinib (LENVIMA; Eisai Co., Ltd., Tokyo, Japan) for thyroid cancer at Ito Hospital from April 2015 through September 2018 were consecutively enrolled in this study. The inclusion criteria were in accordance with standard eligibility criteria for lenvatinib treatment [14]. Forty-six Japanese patients (32 women and 14 men) were analyzed in this study; however, 4 patients were excluded because of adverse events just after beginning (2 patients) and not meeting inclusion criteria (2 patients). The follow-up phase was 3 years. Patient characteristics prior to lenvatinib therapy are listed in Table 1. The mean age was 64 ± 13 years, and the mean body weight was 56 ± 13 kg. There were no patients with serious renal or hepatic dysfunction. The study was approved by the Ethics Committees of Ito Hospital (approval no. 137) and Akita University School of Medicine (approval no. 790) and was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Patients provided written informed consent for participation in the study.

Table 1 Demographic and clinical characteristics of patients prior to lenvatinib therapy

Female: male	32:14	
Age (years)	64 ± 10	(33–82)
Body weight (kg)	56 ± 13	(34–94)
Body surface area (m^2)	1.60 ± 0.20	(1.24–2.15)
Laboratory test values		
White blood cell ($/mm^3$)	5786 ± 1592	(3000–10,500)
Red blood cell ($\times 10^4/mm^3$)	452 ± 53	(308–557)
Platelet ($\times 10^4/mm^3$)	18.7 ± 7.0	(4.4–34.7)
Aspartate transaminase (IU/L)	31 ± 13	(16–81)
Alanine transaminase (IU/L)	29 ± 18	(11–87)
Serum albumin (g/dL)	3.9 ± 0.4	(3.1–4.8)
Total bilirubin (mg/dL)	0.7 ± 0.2	(0.3–1.2)
Serum creatinine (mg/dL)	0.74 ± 0.28	(0.41–1.66)
UGT1A1 genotype		
1/*1*:1/*6*:**1/*28*:**6/*6*:**6/*28*:*unknown*	17:8:8:1:3:9	

Data are presented as the mean ± standard deviation (range) or number (%)

All patients received oral lenvatinib 24 mg once daily as an initial dose. Sequential dose reductions to 20, 14, 10, 8, and 4 mg/day were conducted based on the grade of each side effect according to a guide in the package insert [14]. The toxicity grade was determined based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Plasma samples were collected within ± 4 h at 24 h after lenvatinib administration, and the steady-state trough plasma concentration (C_0) was defined as the concentration for samples collected within ± 4 h of the scheduled time every 2 weeks for the first 3 months after beginning lenvatinib therapy and then every 1 month for up to 3 years. Blood samples, except at a sampling time of 24 ± 4 h after administration and for samples within 7 days (that had not achieved steady-state) after changing the daily dose, were excluded from analysis. In addition, unclear data for the ingestion time of lenvatinib were excluded. For every hospital visit, clinical evaluation or assessment of adverse events by CTCAE, assay of lenvatinib C_0, and biochemical evaluation were performed at the same time of day and were retrospectively analyzed. Plasma was isolated by centrifugation at 1900×*g* for 15 min and was stored at − 40 °C until analysis.

Pharmacokinetics analysis

Plasma trough concentrations of lenvatinib were measured by high-performance liquid chromatography and ultraviolet

analysis (HPLC–UV), as previously described [15]. The calibration curve generated for lenvatinib in human plasma was linear over the concentration range of 5 to 1000 ng/mL. The limit of quantification of lenvatinib for this assay was 5 ng/mL. The coefficients of variation (CVs) and accuracies for intra- and interday assays at the concentration range of 5 to 1000 ng/mL were less than 12.6% and within 10.6%, respectively.

Genotyping

DNA was extracted from peripheral blood samples using a QIAamp Blood Kit (Qiagen, Hilden, Germany) and was stored at − 80 °C until analysis. We studied the following variant sequences: a 2-nucleotide insertion (TA) within the TATA box resulting in the sequence $(TA)_7TAA$ (*UGT1A1*28*, rs8175347) and a transition at codon 71 in exon 1 that changed glycine to arginine (*UGT1A1*6*, rs4148323). Genotyping procedures to identify the *UGT1A1*6* and **28* alleles were performed using polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP) [13]. Furthermore, the results of PCR–RFLP were confirmed using an automated single nucleotide polymorphism detection system (i-densy; ARKRAY Inc., Kyoto, Japan). *UGT1A1* genotype analysis revealed five different patterns, as follows: **1/*1* in 17 patients, **1/*6* in 8 patients, **1/*28* in 8 patients, **6/*6* in 1 patient, and **6/*28* in 3 patients. Based on these results, patients were divided into three groups: *UGT1A1*1/*1* ($n = 17$), **1/*6 + *1/*28* ($n = 16$), and **6/*6 + *6/*28* (PMs; $n = 4$; Table 1).

Statistical analyses

Shapiro–Wilk tests were used to assess distributions. Spearman's rank correlation coefficient values were used to assess correlations between continuous values. To evaluate the relationships between lenvatinib C_0 and safety variables, laboratory test data were compared among the three groups based on the quartile (Q) of lenvatinib C_0 distribution. Kruskal–Wallis tests were used to compare continuous values for more than three groups, and median values in the different groups were compared using Mann–Whitney *U* tests with Bonferroni's correction. The Wilcoxon signed-rank test was used to determine differences in continuous values for each patient. Results with *P* values of less than 0.05 were considered statistically significant in correlation coefficient tests and multiple comparison tests. In contrast, results with *P* values of less than 0.05/3 were considered statistically significant in comparison between two groups after comparison between three groups. Statistical analysis was performed with SPSS 20.0 for Windows (SPSS IBM Japan Inc., Tokyo, Japan). For post hoc power analysis, the effect size calculated in comparison with the lenvatinib C_0 between UGT1A1 genotypes differed significantly. Power was calculated using G*Power ver. 3.1 software.

Results

We collected 445 plasma samples from 46 patients in this study. The C_0 of lenvatinib increased significantly and proportionately across daily doses ranging from 4 to 24 mg ($r = 0.505$, $P < 0.001$), although there was very large inter-patient variability among patients treated with the same daily dose of lenvatinib (Fig. 1). From all plasma samples, the mean and median (minimum–maximum) C_0 values of lenvatinib at the steady-state after administration of 8, 10, 14, 20, and 24 mg/day were 43.4 and 42.0 (10–88) ng/mL ($n = 53$, CV = 42%), 54.6 and 47.0 (14–162) ng/mL ($n = 134$, CV = 54.7%), 75.0 and 68.0 (16–186) ng/mL ($n = 79$, CV = 55.5%), 107 and 89.5 (25–228) ng/mL ($n = 56$, CV = 52.0%), and 95.6 and 83.0 (24–233) ng/mL ($n = 49$, CV = 48.2%), respectively (Fig. 1).

Time-dependent changes in the C_0 and daily dose of lenvatinib after beginning therapy are shown in Fig. 2. Dose reduction from 24 mg daily was carried out according to the onset of adverse events, and the C_0 of lenvatinib was rapidly reduced over time (Fig. 2a, b). The median (range) duration of lenvatinib therapy was 380 (41–1121) days, and the numbers of patients continuing therapy less than 1, 1–2, and 2–3 years were 20, 12, and 14, respectively.

The relationship between the grades of lenvatinib-induced adverse events classified by CTCAE with the lenvatinib C_0 is shown in Fig. 3. There were no significant differences in lenvatinib C_0 values according to CTCAE grades for hypertension, proteinuria, hand-foot syndrome, and diarrhea. In

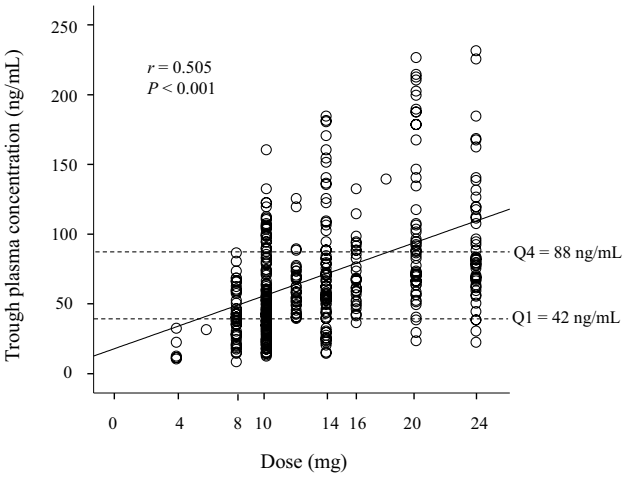

Fig. 1 The relationships between daily dose and trough plasma concentration of lenvatinib. *Q* quartile

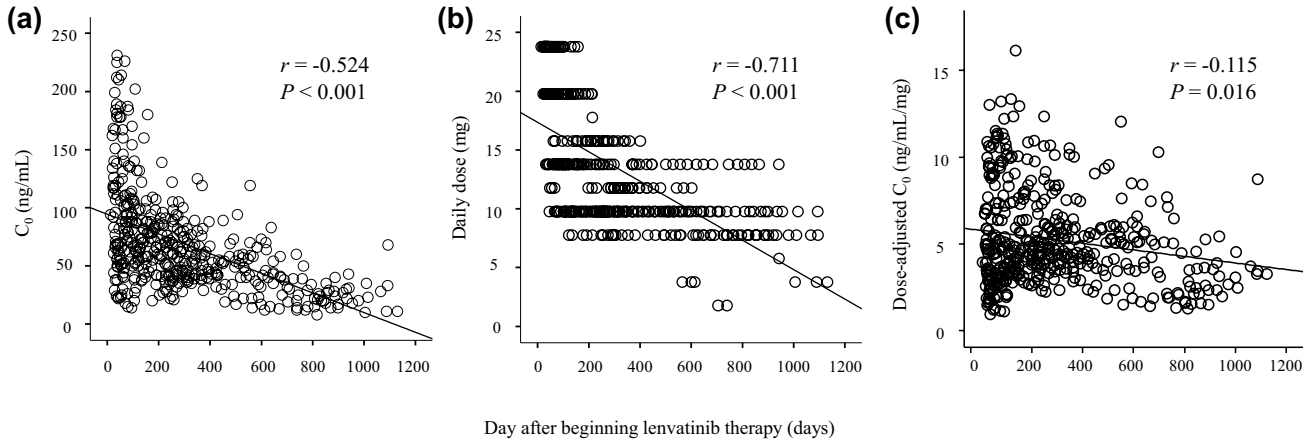

Fig. 2 Time-dependent changes in trough plasma concentrations (**a**) and daily doses (**b**) and dose-adjusted trough plasma concentrations (**c**) of lenvatinib after beginning therapy

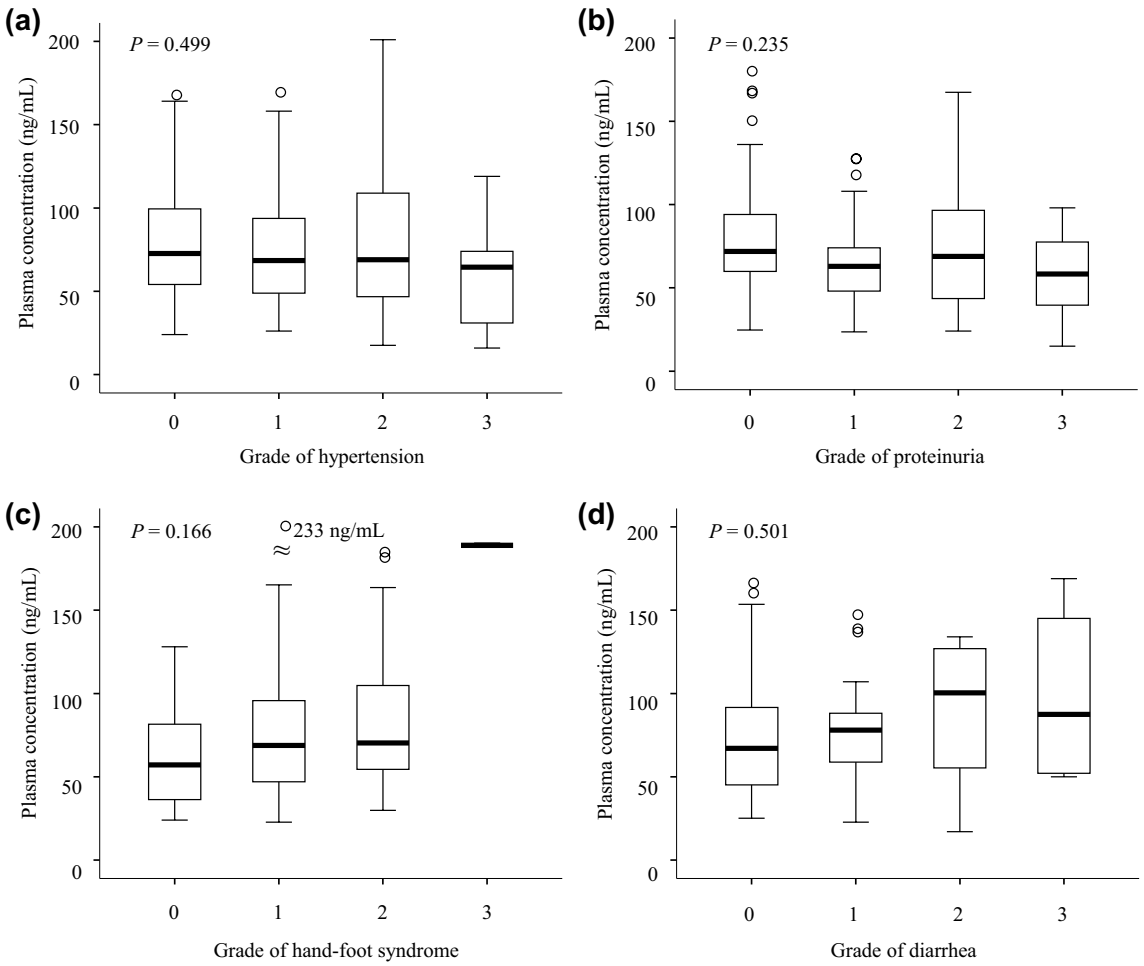

Fig. 3 Relationship between grades of lenvatinib-induced hypertension (**a**), proteinuria (**b**), hand-foot syndrome (**c**), and diarrhea (**d**) classified by CTCAE with trough plasma concentrations of lenvatinib using a box and whiskers plot. The box spanned data between two quartiles (IQR), with the median represented as a bold horizontal line. The ends of the whiskers (vertical lines) represent the smallest and largest values that are not outliers. Outliers (circle) are values between 1.5 and 3 IQRs from the end of the box

addition, the relationships between lenvatinib C_0 and systolic or diastolic blood pressure are shown in Fig. 4. There were no significant differences between lenvatinib C_0 values and the blood pressure of patients.

The potential relationships between lenvatinib C_0 values and safety variables were explored according to observed lenvatinib C_0 values categorized into quartile (Q) groups (Table 2). The incidences of biochemical abnormalities, such as changes in aspartate transaminase, alanine transaminase, serum albumin, and total bilirubin levels, were significantly lower in the lenvatinib C_0 Q1 (< 42 ng/mL) group compared with those in the Q4 (≥ 88 ng/mL) group. In contrast, platelet counts in patients were highest in the lowest Q1 group (Table 2). The influence of total bilirubin levels and aspartate transaminase on changes (from maximum to minimum values) in lenvatinib C_0 for individual patients is shown in Fig. 5. The degradation of bilirubin levels was observed, as reflected by reduced lenvatinib C_0 values.

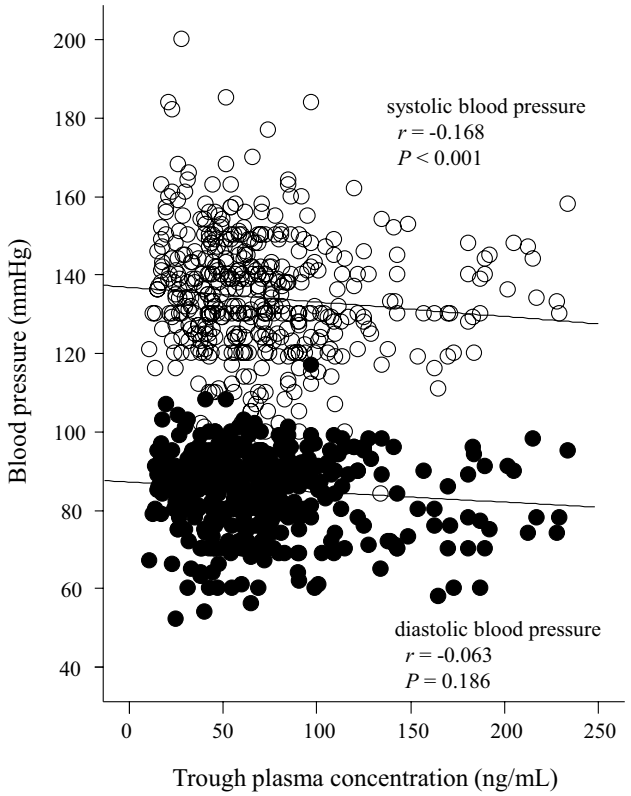

Fig. 4 Relationships of systolic (opened circles) and diastolic (closed circles) blood pressure with trough plasma concentrations of lenvatinib

Comparisons of the daily doses and C_0 values of lenvatinib and the total bilirubin levels among *UGT1A1* genotypes are shown in Table 3. The median daily dose of lenvatinib in *UGT1A1* PMs was significantly lower than that in patients with *UGT1A1*1/*1* (10 and 14 mg, respectively; effect size = 0.335), whereas the median total bilirubin level was significant higher in *UGT1A1* PMs (0.9 and 0.5 mg/dL, respectively; effect size = 1.000). There were no significant differences in median lenvatinib C_0 values between patients with *UGT1A1*1/*1* and PMs (58.0 and 50.0 ng/mL, respectively; effect size = 0.997).

Discussion

In the current study, all patients received lenvatinib 24 mg once daily as an initial dose; however, all patients required dose reduction owing to onset of adverse events within 150 days after beginning lenvatinib therapy. This was consistent with a previous report showing that the time to first dose reduction was 4.4 months after beginning of lenvatinib therapy [6]. Thus, in the maintenance phase at 1 year after administration of lenvatinib, the daily dose of lenvatinib for many patients is in the range from 8 to 14 mg. Notably, in the present study, the C_0 of lenvatinib was rapidly reduced

Table 2 Comparison of laboratory test data among quartiles of lenvatinib trough plasma concentrations

Lenvatinib plasma concentration	Q1 (< 42 ng/mL)		Q2–3 (42 ≤ , 88 > ng/mL)		Q4 (88 ng/mL ≤)		$P^{\$}$
Laboratory test	Median	(Q1–Q3)	Median	(Q1–Q3)	Median	(Q1–Q3)	
White blood cell (/mm^3)	5370	(4600–5990)	5300	(4550–6200)	5300	(4480–6700)	0.618
Red blood cell (× 10^4/mm^3)	459	(407–475)	447	(407–473)	442	(422–474)	0.432
Platelet (× 10^4/mm^3)	19.4	(16.2–23.0)	18.6	(15.0–22.4)	17.6*	(13.0–21.1)	0.008
Aspartate transaminase (IU/L)	25	(21–28)	24	(21–30)	28*,#	(23–35)	< 0.001
Alanine transaminase (IU/L)	19	(15–25)	19	(15–26)	24*,#	(17–34)	0.000
Serum albumin (g/dL)	3.7	(3.4–4.3)	3.8	(3.4–4.2)	3.9*	(3.7–4.3)	0.025
Total bilirubin (mg/dL)	0.5	(0.4–0.7)	0.6	(0.4–0.8)	0.7*,#	(0.6–0.9)	< 0.001
Serum creatinine (mg/dL)	0.73	(0.59–0.98)	0.74	(0.62–0.89)	0.69	(0.55–0.88)	0.240

Q quartile

*And #$P < 0.05/3$; *Q4 versus Q1; #Q4 versus Q2–3 (by using Mann–Whitney *U* test)

$Multiple comparisons among Q1 versus Q2–3 versus Q4 (by using Kruskal–Wallis test)

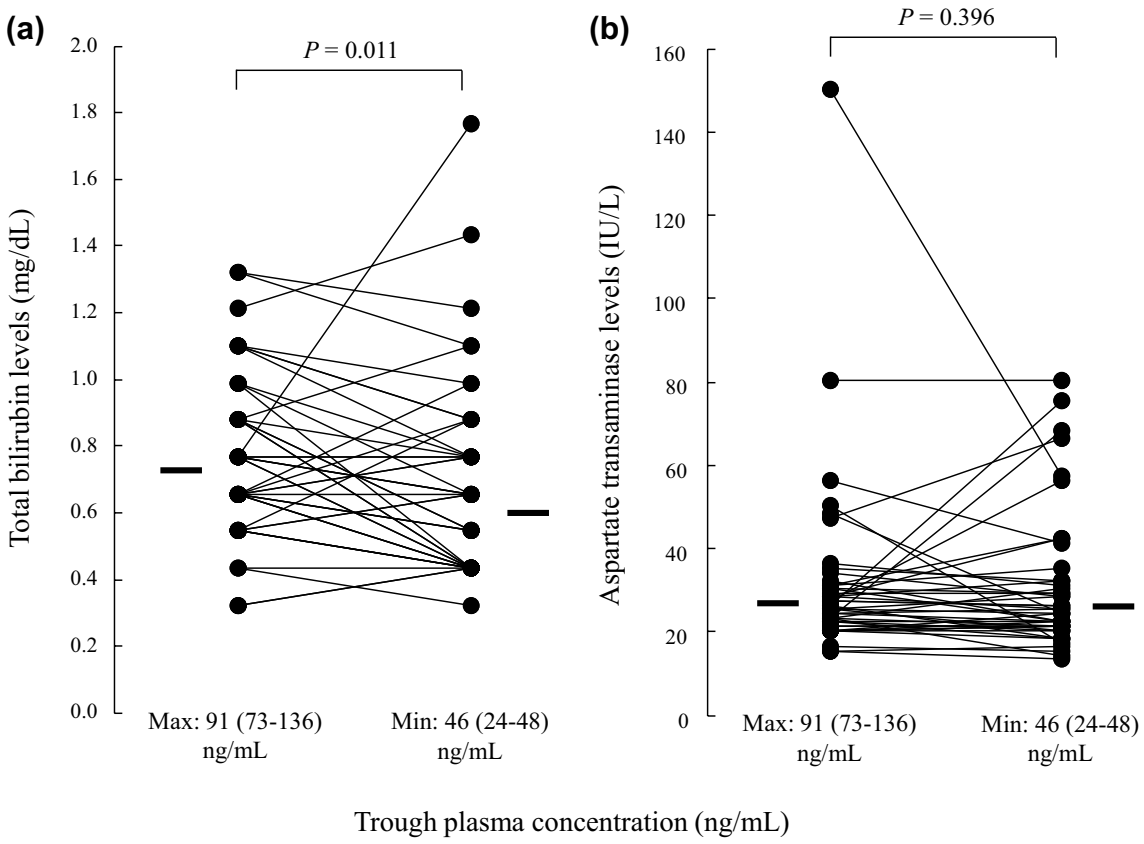

Fig. 5 Changes in the total bilirubin levels (**a**) and aspartate transaminase levels (**b**) between minimum (Min) and maximum (Max) values of trough plasma concentrations of lenvatinib. Crossbar: median value

Table 3 Comparison of daily dose of lenvatinib, trough plasma concentration of lenvatinib, and total bilirubin levels among *UGT1A1* genotypes

	UGT1A1 genotype	Median	(Q1–Q3)	*P*
Daily dose (mg)	**1/*1*	14	(10–20)	0.001
	**1/*6 + *1/*28*	12*	(10–16)	
	**6/*6 + *6/*28*	10*,#	(10–14)	
Trough plasma concentration (ng/mL)	**1/*1*	58.0	(42.0–72.5)	< 0.001
	**1/*6 + *1/*28*	68.0*	(44.0–96.0)	
	**6/*6 + *6/*28*	50.0#	(36.0–73.0)	
Total bilirubin (mg/dL)	**1/*1*	0.5	(0.4–0.6)	< 0.001
	**1/*6 + *1/*28*	0.6*	(0.5–0.7)	
	**6/*6 + *6/*28*	0.9*,#	(0.7–1.1)	

Q quartile

*And #*P* < 0.05/3; *versus *UGT1A1*1/*1*; #versus *UGT1A1*1/*6 + *1/*28*

over time. In patients with a higher lenvatinib C_0, the levels of aspartate transaminase, alanine transaminase, serum albumin and total bilirubin were significantly higher, and platelet counts were significantly lower than those in patients with a lower C_0. By lowering the lenvatinib C_0, degradation of bilirubin levels was observed. However, there were no significant differences in lenvatinib C_0 values in patients with different CTCAE grades of hypertension, proteinuria, hand-foot syndrome, and diarrhea induced by lenvatinib.

The target C_0 of lenvatinib is approximately 51.5 ng/mL based on the mean C_0 at the steady-state in a phase 3 trial [7, 8]. However, until now, no studies have reported the thresholds between the C_0 of lenvatinib and responses or toxicities of lenvatinib in the clinical setting. In the current study, the Q1 of the lenvatinib C_0 at the steady-state was less than

42 ng/mL, and the Q4 was more than 88 ng/mL. Because there were no significant differences in laboratory evidence between Q1 (< 42 ng/mL) and Q2–3 (42–88 ng/mL) groups for lenvatinib C_0, the target C_0 for lenvatinib as the threshold between the C_0 and optimal response may range from 42 to 88 ng/mL. In addition, in the maintenance phase at 2 years after administration of lenvatinib, the C_0 values of lenvatinib were approximately 42 ng/mL. Therefore, similar to previous reports [7, 8], the threshold between C_0 and optimal response to lenvatinib may be approximately 51.5 ng/mL. In contrast, the threshold between the C_0 and toxicity of lenvatinib may be more than 88 ng/mL. Consequently, the results of the current study suggested that the dose of lenvatinib should be regulated to maintain a lower C_0 of less than 88 ng/mL.

Many KIs inhibit UGT1A1 [16]. Lenvatinib is also a weak inhibitor of UGT1A1 [8]. This first report of *UGT1A1* PMs showed an elevated risk of lenvatinib-induced hyperbilirubinemia in these patients. Importantly, in this study, the dose of lenvatinib was controlled by confirming laboratory evidence or adverse events, and accordingly, total bilirubin levels in all patients were controlled to less than 1.5 mg/dL during lenvatinib therapy. As a result of hyperbilirubinemia, the median daily dose of lenvatinib in patients with the *UGT1A1*6/*6* or **6/*28* genotype was 10 mg/day, which was lower than that for patients with the *UGT1A1*1/*1*, **1/*6*, or **1/*28* genotype (12–14 mg/day). Although the median daily dose of lenvatinib for *UGT1A1* PMs was low (10 mg), bilirubin levels were significantly higher than those in patients with the *UGT1A1*1* allele. Thus, information regarding *UGT1A1* polymorphism before beginning lenvatinib therapy may be useful; however, the inhibitory activity of lenvatinib on UGT1A1 does not seem to be so strong, in contrast to that of other KIs [16, 17]. Lenvatinib therapy may be continued by using low doses for present hyperbilirubinemia.

An increase in the incidences of hypertension and proteinuria (grade 3 or higher), with increased area under the plasma concentration (AUC) for lenvatinib has been reported in phase II and III studies of lenvatinib [8]. In particular, the incidence of grade 3 or higher hypertension tends to be higher in Japanese patients than in non-Japanese patients [8]. Because hypertension is a known side effect of KIs that target the VEGF pathway [5], it is likely that hypertension is related to the AUC of lenvatinib. However, in the current study, hypertension and proteinuria were not related to the C_0 of lenvatinib. Accordingly, in our study, the plasma concentrations on day 1 and at 24 h after initial administration (C_{24} on day 1 or C_0 on day 2) were not monitored, and assessment of lenvatinib-induced adverse events and assay of lenvatinib C_0 values at steady-state were evaluated beginning 2 weeks after initiation of lenvatinib 24 mg/day. Therefore, similar to phase II and III studies of lenvatinib [8], the correlations between plasma concentrations and toxicities of lenvatinib during the early phase ($AUC_{0–24}$ or C_{24} on day 1) after lenvatinib therapy may be evaluated. Further studies are needed to determine the relationships between lenvatinib-induced adverse events, such as hypertension, and C_0 values at the same time of day.

Our results could be interpreted within the context of the study limitations. In the current study, we collected 445 plasma samples from 46 patients. When we investigated laboratory data and the onset of side effects at the same time as analysis of lenvatinib plasma concentrations from one patient sequentially, there may have been some bias in our results. Among the 46 patients in our analysis, 14 patients took lenvatinib for more than 2 years. Thus, the small number of patients taking lenvatinib for a long time may have resulted in bias in the results. Therefore, additional studies having larger sample sizes are necessary. However, no reports have completely linked laboratory data, the onset of side effects, and plasma concentrations of lenvatinib at the same time until now. Accordingly, we believe that our current results may have future clinical applications.

Conclusion

There were no significant differences in lenvatinib C_0 values according to CTCAE grades for hypertension, proteinuria, hand-foot syndrome, and diarrhea; however, in patients with a higher lenvatinib C_0, the values for aspartate transaminase, alanine transaminase, serum albumin, and total bilirubin were significantly higher, whereas platelet counts were significantly lower than those in patients with a lower C_0. The threshold between the C_0 and toxicity of lenvatinib appeared to be more than 88 ng/mL. Accordingly, it may be necessary to regulate the dose of lenvatinib in order to maintain a lower C_0 of less than 88 ng/mL.

Acknowledgements This work was supported by a (Grant No. 17K08408) from the Japan Society for the Promotion of Science, Tokyo, Japan.

Disclosure All authors report that they have no relevant relationships to disclose.

Authors' contribution MN, TO, AS, KS, KI, and MM participated in the design of the study and reviewed the results. MN, AS, KS, and KI were responsible for the patient collection and involved in acquisition of data. TO carried out genotyping. MM analyzed plasma concentrations. TN and MM were responsible for the statistical analysis. MN, TO, and MM drafted the manuscript. AS, KS, TN, and KI helped to draft the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest All authors have no conflicts of interest.

Research involving human participants The study was performed in accordance with the ethical standards of the Declaration of Helsinki and its subsequent amendments.

Informed consent Signed informed consent was obtained from all patients.

References

1. Matsui J, Yamamoto Y, Funahashi Y, Tsuruoka A, Watanabe T, Wakabayashi T, Uenaka T, Asada M. E7080, a novel inhibitor that targets multiple kinases, has potent antitumor activities against stem cell factor producing human small cell lung cancer H146, based on angiogenesis inhibition. Int J Cancer. 2008;122:664–71.
2. Okamoto K, Kodama K, Takase K, Sugi NH, Yamamoto Y, Iwata M, Tsuruoka A. Antitumor activities of the targeted multi-tyrosine kinase inhibitor lenvatinib (E7080) against RET gene fusion-driven tumor models. Cancer Lett. 2013;340:97–103.
3. Yamamoto Y, Matsui J, Matsushima T, Obaishi H, Miyazaki K, Nakamura K, Tohyama O, Semba T, Yamaguchi A, Hoshi SS, Mimura F, Haneda T, Fukuda Y, Kamata JI, Takahashi K, Matsukura M, Wakabayashi T, Asada M, Nomoto KI, Watanabe T, Dezso Z, Yoshimatsu K, Funahashi Y, Tsuruoka A. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. Vasc Cell. 2014;6:18.
4. Tohyama O, Matsui J, Kodama K, Hata-Sugi N, Kimura T, Okamoto K, Minoshima Y, Iwata M, Funahashi Y. Antitumor activity of lenvatinib (e7080): an angiogenesis inhibitor that targets multiple receptor tyrosine kinases in preclinical human thyroid cancer models. J Thyroid Res. 2014;2014:638747.
5. Agarwal M, Thareja N, Benjamin M, Akhondi A, Mitchell GD. Tyrosine kinase inhibitor-induced hypertension. Curr Oncol Rep. 2018;20:65.
6. Brose MS, Worden FP, Newbold KL, Guo M, Hurria A. Effect of age on the efficacy and safety of lenvatinib in radioiodine-refractory differentiated thyroid cancer in the phase III SELECT trial. J Clin Oncol. 2017;35:2692–9.
7. Verheijen RB, Yu H, Schellens JHM, Beijnen JH, Steeghs N, Huitema ADR. Practical recommendations for therapeutic drug monitoring of kinase inhibitors in oncology. Clin Pharmacol Ther. 2017;102:765–76.
8. Food and Drug Administration. Center for Drug Evaluation and Research Lenvatinib Clinical Pharmacology and Biopharmaceutics Review. 2014. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206947Orig1s000ClinPharmR.pdf.
9. Bosma PJ, Seppen J, Goldhoorn B, Bakker C, Oude Elferink RP, Chowdhury JR, Chowdhury NR, Jansen PL. Bilirubin UDP-glucuronosyltransferase 1 is the only relevant bilirubin glucuronidating isoform in man. J Biol Chem. 1994;269:17960–4.
10. Bosma PJ. Inherited disorders of bilirubin metabolism. J Hepatol. 2003;38(1):107–17.
11. Bosma PJ, Chowdhury JR, Bakker C, Gantla S, de Boer A, Oostra BA, Lindhout D, Tytgat GN, Jansen PL, Oude Elferink RP, Chowdhury NR. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. N Engl J Med. 1995;333:1171–5.
12. Beutler E, Gelbart T, Demina A. Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism? Proc Natl Acad Sci USA. 1998;95:8170–4.
13. Ando Y, Saka H, Ando M, Sawa T, Muro K, Ueoka H, Yokoyama A, Saitoh S, Shimokata K, Hasegawa Y. Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. Cancer Res. 2000;60:6921–6.
14. LENVIMA (Lenvatinib). Drug interview form (Package insert). Tokyo: Eisai Co., Ltd; 2015.
15. Miura M, Sato K, Miura H, Niioka T, Kobayashi H, Narita C, Ito H. A limited sampling strategy for estimation of the area under the plasma concentration-time curve of gefitinib. Ther Drug Monit. 2014;36:24–9.
16. Fujita K, Sugiyama M, Akiyama Y, Ando Y, Sasaki Y. The small-molecule tyrosine kinase inhibitor nilotinib is a potent noncompetitive inhibitor of the SN-38 glucuronidation by human UGT1A1. Cancer Chemother Pharmacol. 2011;67:237–41.
17. Miura M. Therapeutic drug monitoring of imatinib, nilotinib, and dasatinib for patients with chronic myeloid leukemia. Biol Pharm Bull. 2015;38:645–54.