Acta Med. Okayama, 2024
Vol. 78, No. 1, pp. 63–70

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

Significance of Continuous Low-Dose Lenvatinib for the Treating of the Patients with Unresectable Thyroid Carcinoma

Daizo Murakami[a], Kohei Nishimoto[a], Soshi Takao[b], Satoru Miyamaru[a], Tomoka Kadowaki[b], Haruki Saito[a], Hiroki Takeda[a], Momoko Ise[a], Koichi Suyama[c], and Yorihisa Orita[a]*

[a]Department of Otolaryngology-Head and Neck Surgery, Kumamoto University Graduate School of Medicine, Kumamoto 860-8556, Japan, [b]Department of Epidemiology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan, [c]Department of Medical Oncology, Toranomon Hospital, Tokyo 105-8470, Japan

The tyrosine kinase inhibitor lenvatinib has been confirmed as an effective treatment option for patients with unresectable thyroid carcinoma. We conducted a retrospective analysis of the significance of the effect of continued lenvatinib treatment for the longest duration possible at a reasonable daily dose and with a minimum discontinuation period in 42 patients with unresectable thyroid carcinoma treated with lenvatinib between 2015 and 2020. A Cox proportional hazard model-based analysis revealed that the overall survival of the patients treated with a < 8 mg/day mean dose of lenvatinib was significantly better than that of the patients treated with 8-24 mg/day (hazard ratio [HR] 0.38 for 1.14-4.54 mg/day, and HR 0.01 for 4.56-7.97 mg/day) adjusted for various factors (*e.g.*, sex, age, drug interruption period). The cumulative dose of lenvatinib administered tended to be higher in the patients treated with low doses (< 8 mg/day) than in the patients treated with relatively high doses (8-24 mg/day). Considering its adverse events, the continuation of lenvatinib treatment with an adequate daily dose and drug interruption may help prolong the survival of patients with unresectable thyroid carcinoma.

Key words: thyroid carcinoma, lenvatinib, adverse effect, survival

The phase III Study of Lenvatinib in Differentiated Cancer of the Thyroid (SELECT) demonstrated that treatment with lenvatinib—an oral, multitargeted tyrosine kinase inhibitor (TKI)—prolonged the disease progression-free survival (PFS) of patients with radioactive iodine (RAI)-refractory differentiated thyroid carcinoma. In addition, following the results of a phase II trial conducted in Japan, lenvatinib was approved for the treatment of patients with unresectable thyroid carcinoma of all histological subtypes [1-4]. However, in the SELECT trial, 97.3% of the total number of patients (n = 261) and 100% of the Japanese patients (n = 30) treated with lenvatinib presented with adverse effects (AEs) such as hypertension, diarrhea, loss of appetite, proteinuria, or hand-foot syndrome [1]. Specifically, patients at older ages and those with a poorer performance status (PS) can experience higher lenvatinib toxicity [5]. Although the recommended dose of lenvatinib was established as 24 mg once daily, most patients in daily clinical practice cannot continue treatment with lenvatinib at the starting dose, mostly due to the occurrence of diarrhea, hypertension, or proteinuria [6]. Hypertension induced by lenvatinib was also reported

Received April 3, 2023; accepted October 6, 2023.
*Corresponding author. Phone: +81-96-373-5255; Fax: +81-96-373-5256
E-mail: yoriorita@kumamoto-u.ac.jp (Y. Orita)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

to be more frequent in patients aged ≥75 years, and it was suggested that early blood-pressure control might be an effective approach to maintain the lenvatinib dose intensity [7]. Yamazaki *et al.* defined the flare phenomenon as death, hospitalization attributable to tumor progression, or an unexpected event (*e.g.*, pleural drainage) within 1 month of lenvatinib cessation; they observed that the patients' overall survival (OS) tended to be poorer in the flare group compared to the non-flare group [8]. The incidence of flare phenomenon in their patients was 14.3%, and the median time from lenvatinib cessation to the occurrence of flare phenomenon was 9 days [8]. Therefore, in daily clinical practice, maintenance of the highest reasonable dose of lenvatinib with a minimum discontinuation period is the chief objective. The American Thyroid Association (ATA) guidelines state that patients who are candidates for TKI therapy "should be thoroughly counseled on the potential risks and benefits of the treatment as well as alternative therapeutic approaches including best supportive care" [9].

At our institution, we have made efforts to continue the lenvatinib treatment of patients with unresectable thyroid carcinoma for the longest duration possible with a reasonable daily dose and interruption period. We conducted the present study to retrospectively analyze the significance of the effect of continued lenvatinib treatment for the longest duration possible at a reasonable daily dose and with a minimum discontinuation period.

Patients and Methods

During the period from September 2015 to March 2020, 42 patients with unresectable thyroid carcinoma, including 35 patients with papillary thyroid carcinoma (PTC), three with follicular thyroid carcinoma (FTC), and four with anaplastic thyroid carcinoma (ATC) were treated with lenvatinib at Kumamoto University Hospital, a tertiary oncology referral center in Kumamoto, Japan. The clinical characteristics of the 42 patients are summarized in Table 1. The 42 patients comprised 17 men (40.5%) and 25 women (59.5%). The mean age at the initiation of lenvatinib treatment was 71 years (range 43-91 years). The PS was 0 in 27 patients, 1 in 10 patients, and 2 in five patients. The

Table 1 Clinical characteristics

		Total		Daily dose tertiles						*P-value*
				Q1: 1.14–4.54 mg		Q2: 4.56–7.97 mg		Q3: 8–24 mg		
		n=42		n=14		n=14		n=14		
Age (years old)		71.0 (43–91)		78.0 (49–91)		66.5 (43–85)		67.0 (54–81)		*0.0163*
Sex	Male	17	40.5%	3	21.4%	5	35.7%	9	64.3%	*0.0628*
	Female	25	59.5%	11	78.6%	9	64.3%	5	35.7%	
PS	0	27	64.3%	12	85.7%	8	57.1%	7	50.0%	*0.1093*
	1	10	23.8%	0	0.0%	4	28.6%	6	42.9%	
	2	5	11.9%	2	14.3%	2	14.3%	1	7.1%	
BMI		22.0 (15.2–32.1)		22.7 (17–32.1)		22.3 (16.9–18.2)		21.4 (15.2–27.0)		*0.5285*
RAI therapy	yes	29	69.0%	12	85.7%	10	71.4%	7	50.0%	*0.1204*
	no	13	31.0%	2	14.3%	4	28.6%	7	50.0%	
Reccurence										
local		5	11.9%	2	14.3%	1	7.1%	2	14.3%	*0.7969*
local + distant		11	26.2%	3	21.4%	5	35.7%	3	21.4%	
distant		26	61.9%	9	64.3%	8	57.1%	9	64.3%	
Contact with major arteries										
yes		7	18.9%	0	0.0%	2	16.7%	5	41.7%	*0.0284*
no		30	81.1%	13	100%	10	83.3%	7	58.3%	
Histology										
papillary ca		35	83.3%	14	100.0%	11	78.6%	10	71.4%	*0.1817*
follicular ca		3	7.1%	0	0.0%	2	14.3%	1	7.1%	
anaplastic thyroid ca		4	9.5%	0	0.0%	1	7.1%	3	21.4%	
Initial dose (Median, mg/day)		24 (10–24)		24 (14–24)		24 (10–24)		24 (10–24)		*0.4175*
Mean dose (mg/day)		6.825 (1.14–24.00)		2.80 (1.14–4.54)		6.825 (4.56–7.97)		11.71 (8.00–24.00)		*<0.0001*
Cumulative dose (mg)		2,371 (81–12,434)		2,371 (81–5,474)		2,977 (476–11,510)		1,326 (188–12,434)		*0.2717*
Rest period (%)		34.3 (0–92.6)		51.6 (22.2–92.6)		27.1 (5.4–64.2)		26.2 (0–62.4)		*0.0012*

mean body mass index (BMI) was 22.0 (range 15.2-32.1). A total of 29 patients (69.0%) had undergone RAI therapy. Five patients (11.9%) presented with unresectable local tumors, 11 (26.2%) presented with both local and distant lesions, and 26 (61.9%) presented with only distant metastases. In seven patients (18.9%), at least one lesion was observed to be in contact with a major artery. In these seven patients, lenvatinib was used after an explanation was provided to and discussed with the patients and their family members, and after the performance of multiple imaging studies. The mean duration of follow-up for surviving patients after the commencement of lenvatinib treatment was 592 days (range 23-1,736 days).

Depending on the condition of each patient, the starting dose of the lenvatinib was 24 mg in 34 patients, 20 mg in one patient, 14 mg in five patients, and 10 mg in two patients. The dose was reduced or treatment was interrupted or discontinued according to the patient's condition; the reasons for reduction were contact with major arteries (n = 6), tracheal invasion (n = 1), untreated hypertension (n = 1), advanced age (> 85 years) (n = 1), and PS (n = 2). As a general rule, the starting dose of lenvatinib was set at 24 mg, with a two-stage reduction to 14 mg for patients suspected of having tumor infiltration into major blood vessels such as the carotid artery and for elderly patients > 85 years old, with further adjustments made based on the patient's condition. When the lenvatinib dose was reduced due to side effects, the standard procedure involves a single-stage reduction; however, in one patient who required an extended drug withdrawal period, the dosage was reduced in three stages from 24 mg to 10 mg.

The prognostic factors evaluated included sex, age, PS, BMI, with/without RAI therapy, with/without local tumor, single or multiple lesions, with/without lesions close to a major artery, the starting dose of lenvatinib, the average daily dose, the total administration dose, the frequency and period of discontinuation, the ratio of the total discontinuation period to the total therapeutic period, and AEs. The AEs were evaluated using the Common Terminology Criteria for AEs (CTCAE), ver. 4.0.

The protocol of this study including the opt-out consent method was approved by the Clinical Research Ethics Committee of Kumamoto University (Registry no. 2338) and conformed to the amended Declaration of Helsinki. The need for informed consent was waived in accord with the Committee's instruction, in light of the retrospective nature of the study design. The study information was presented on the Web to provide the opportunity to opt out of this research, which substituted for the participants' consent.

Statistical analyses. We checked the patients' medication status and adherence at each medical consultation. Using the administered lenvatinib dose, the total treatment period (days), and the number of days of drug suspension, we calculated each patient's cumulative dose, the rate of drug interruption, and the mean dose per day (the cumulative dose divided by the total treatment period). We categorized the mean dose for the complete series of 42 patients with unresectable thyroid carcinoma into daily dose tertiles in order to evenly divide the population into three groups (n = 14 in each category) as follows: Q1 (1.14-4.54 mg/day), Q2 (4.56-7.97 mg/day), and Q3 (8.00-24 mg/day). We also categorized the rest period (*i.e.*, the percentage of the period when lenvatinib treatment was tentatively halted to the entire treatment period) into tertiles: Q1 (0-24.84%), Q2 (24.90-39.13%), and Q3 (41.17-92.58%).

We first determined the demographic and clinical characteristics of the patients for both the total series and for the groups stratified by daily dose tertiles (Q1-Q3). We performed a one-way analysis of variance (ANOVA) to compare the average age and BMI values, and we used Pearson's χ^2-test to compare categorical variables among groups. We then obtained Kaplan-Meier survival curves to evaluate the patients' OS and PFS, which were calculated from the dates of the initiation of lenvatinib treatment. The log-rank test and the generalized Wilcoxon test were used to determine significant differences in survival. Values were considered significant at a two-sided p-value < 0.05.

A Cox proportional hazard model was applied to perform adjustments for possible confounding factors. In model 1, we adjusted for age, sex, PS (0 vs. 1-2), and side effects (hand-foot syndrome, hypertension, and proteinuria). In model 2, we adjusted for the rest period in addition to the parameters mentioned for model 1. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. We restricted the adjusted analyses to only differentiated carcinoma (n = 38). All analyses were performed using JMP 15 (SAS, Cary, NC, USA) and Stata/SE 16.1 (StataCorp, College Station, TX, USA) software.

Results

Of the 42 patients with unresectable thyroid carcinoma treated with lenvatinib, 16 (38.1%) succumbed to the disease during the observation period. The death of one patient was attributed to the occurrence of bleeding from large vessels due to fistula formation. According to the response evaluation criteria in solid tumors (RECIST) ver. 1.1, two (4.9%) patients achieved a partial response (PR), 38 (92.7%) patients presented with stable disease (SD), one (2.4%) patient presented with progressive disease (PD), and one patient's response was categorized as not available. No patient achieved a complete response (CR).

As depicted in Fig. 1A, the median OS period after the the commencement of lenvatinib treatment was 1,265 days (range 23-1,736 days; in the patients without ATC [n = 4], 1,399 days). The median PFS period was 855 days (range 15-1,582 days; in the patients without ATC, 765 days) (Fig. 1B). The median therapeutic period was 728 days (in the patients without ATC, 1,015 days). Levatinib treatment was discontinued in 29 (69.0%) of the 42 patients for various reasons: disease progression (n = 13), the development of serious AEs in 11 patients (renal dysfunction/proteinuria [n = 5], pneumonia [n = 1], minor bleeding [n = 1], drug eruption [n = 1], hypertension along with risk of bleeding [n = 1], palpitation [n = 1], thrombocytopenia [n = 1]), leukemia (n = 1); reasons such as economic burden and difficulty in attending hospitals (n = 2), and lost to follow-up (n = 2) (Table 2). Two patients who were on a high dose (20 mg) had to discontinue, one due to disease progression and the other due to AEs, including bradycardia-tachycardia syndrome, congestive heart failure, and interstitial pneumonia. As shown in Fig. 2 and Table 2, a lesion in contact with a major artery, which was one of the reasons to reduce the initial lenvatinib dose, did not cause lenvatinib interruption or termination in any patients.

The median value of the mean dose of lenvatinib in each patient over the entire therapeutic period was 6.8 mg/day (range 1.1-24 mg/day). The median cumulative dose of lenvatinib was 2,371 mg (range 81-12,434 mg). The average frequency of treatment interruption was 14.0 times (range 0-108), and each interruption period spanned 20.6 days (range 0-112 days) on average. The most frequent reasons for treatment interruption the first to third times were hypertension, followed by renal dysfunction/proteinuria, hand-foot syndrome, general fatigue, and thrombocytopenia. Hypertension was the most frequently observed each time: 1st 38.1%, 2nd 25.6%, and 3rd 25.0% (Fig. 2). The average ratio of the total discontinuation period to the total therapeutic period was 34.3% (range 0-92.6%).

Among the various prognostic factors, the patients with PS1 or PS2 were 53 times more likely to succumb than those with PS0 at any given time point after the treatment, assuming that they survived for a specific time; in addition, the cumulative dose of lenvatinib tended to be higher in the patients who received a smaller daily dose (Q1 and Q2 in Table 1) than those who received a larger daily dose; the median cumula-

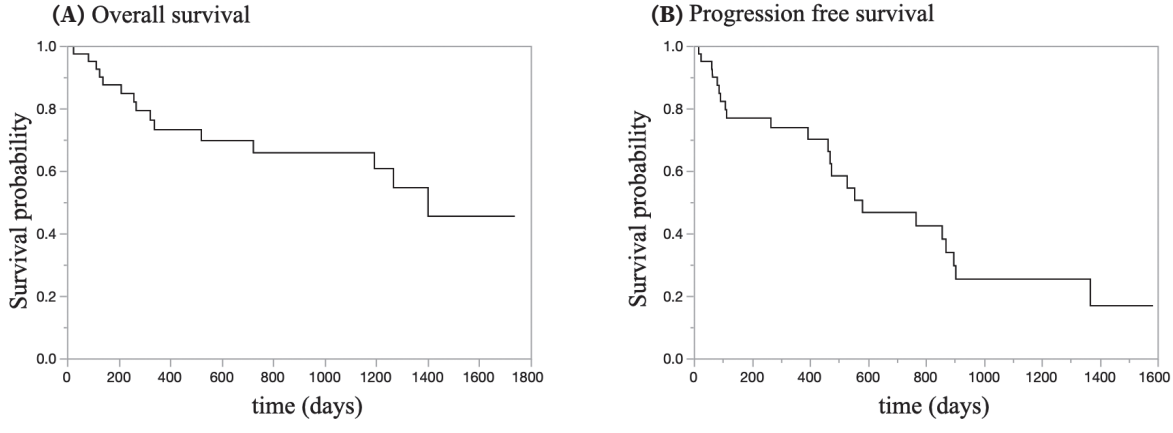

Fig. 1 Kaplan-Meier analysis of (A) overall survival and (B) progression-free survival of the total population of Japanese patients with unresectable thyroid carcinoma (n = 42).

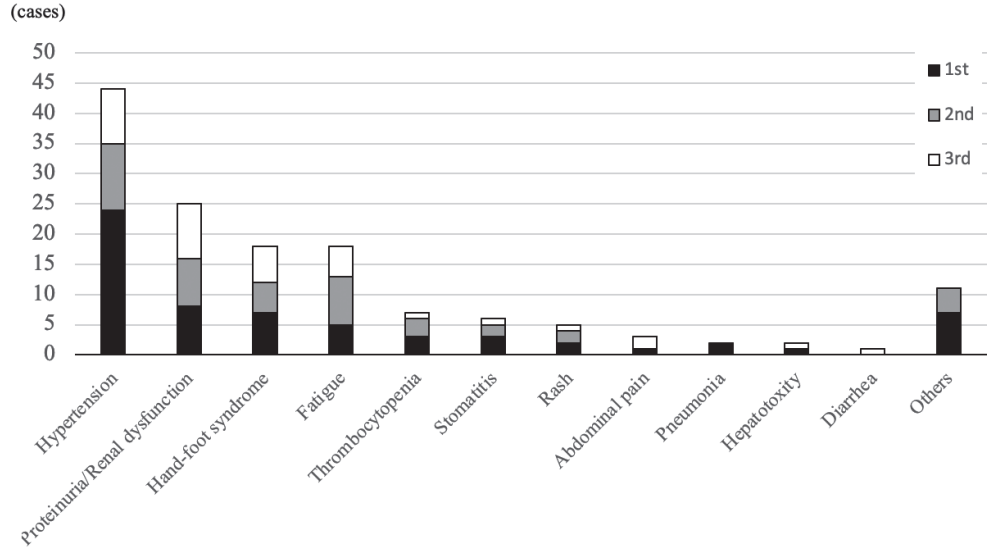

Fig. 2 Reasons for treatment interruption (the first to third times).

Table 2 Reasons of termination of treatment

Progressive disease	13
Adverse effects	
Proteinuria/Renal dysfunction	5
Pneumonia	1
Minor bleeding	1
Drug eruption	1
Hypertension with risk of bleeding	1
Palpitation	1
Thrombocytopenia	1
Onset of other disease (leukemia)	1
Lost to follow up	2
Others*	2
Total	29

*Financial problem, Difficulty in commuting to clinic

tive doses were 2,371 mg in mean-dose Q1 (1.14-4.54 mg/day), 2,977 mg in Q2 (4.56-7.97 mg/day), and 1,326 mg in Q3 (8.00-24 mg/day). With the exclusion of five outlier cases (one patient with a mean dose of 24 mg and four patients with cumulative doses exceeding 8,000 mg), we observed a negative correlation between the cumulative dose and the mean dose ($r = -0.1362$).

Among the patients categorized into tertiles based on different average doses per day, both the OS and PFS of the Q1 (1.14-4.54 mg/day) and Q2 (4.56-7.97 mg/day) patients were significantly better than those of the Q3 patients (8.00-24 mg/day) (Fig. 3A, B), and the results remain unaltered even when values were adjusted for various factors: for the patients' overall survival, HR 0.38, 95%CI: 0.03-4.99 for Q1 and HR 0.01, 95%CI: 0.00-0.13 for Q2 in model 2. For the patients' progression-free survival: HR 0.48, 95%CI: 0.07-3.33 for Q1 and HR = 0.07, 95%CI: 0.01-0.40 for Q2 in model 2. Drug interruption did not tend to have an effect on survival (Table 3).

Based on the analysis of these data excluding the patients with ATC (n = 4), we confirmed that the significant differences were maintained even without ATC (data not shown).

Discussion

Although patients with a lower resistance to adverse event are more likely to opt for an interruption or cessation of lenvatinib treatment [10], in the present series a few patients discontinued the treatment because of the economic burden and challenges involved in visiting hospitals. In a study conducted in the United Kingdom, compared with a placebo or best supportive care, lenvatinib costs more than £50,000 per quality-adjusted life-years (QALY) gained, whereas a cost-effectiveness threshold ranged between £20,000 and 30,000 per QALY [11]. Even in Japan, where a national health insurance program has been established, it is important

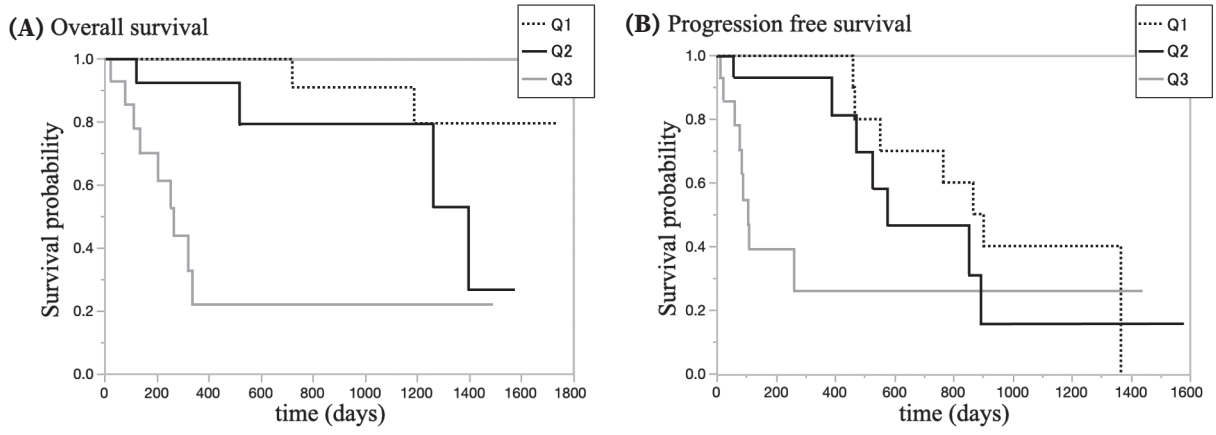

Fig. 3 Kaplan-Meier analysis of the patients' (A) overall survival and (B) progression-free survival by tertiles (Q1–Q3) based on the average daily dose of lenvatinib.

that the benefits of treatment overcome both the economic and somatic burdens of patients in order to ensure the continuation of lenvatinib treatment.

Low-dose lenvatinib treatment can ease both the economic and somatic burdens of patients; moreover, the results of the present study demonstrate that low-dose lenvatinib can be effective at least for Japanese patients, as daily low-dose lenvatinib resulted in prolonged overall survival of the patients. Lenvatinib-emergent hypertension was significantly correlated with improved clinical outcomes [12], and the overall survival benefit has been observed in older patients in whom increased toxicity was observed [5]. In the SELECT trial, hypertension resulted in lenvatinib dose reduction in 19.9% of the patients, and >20% of those hypertensive patients had presented with hypertension within 2 weeks of starting lenvatinib treatment [1]. Since hypertension was the most frequently observed AE resulting in drug interruption in the present study, low-dose lenvatinib treatment may be effective for patients in whom a reduction of the daily dose of lenvatinib is necessary due to the occurrence of AEs. A study conducted in Korea showed that treatment with a sustainable dose of lenvatinib (10 mg/day) helped achieve tumor shrinkage in 90.7% and a PR in 64.7% of the total 43 patients [13].

The standard protocol for lenvatinib treatment is based on data obtained from Western populations, and dose adjustment may thus be necessary for Asian patients because of their smaller physiques [13]. A recent multicenter, randomized clinical trial compared a full initial dose of lenvatinib (24 mg) with 18 mg, and the results revealed that the 24-mg dose produced a better response rate (odds ratio: 0.50, 95%CI: 0.26-0.96) and was accompanied by an increased number of drug interruptions [14]. There has also been a comparison of a full initial dose of lenvatinib with lower initial doses, and the study's authors concluded that a lower initial dose did not reduce the survival rate [15]. With the inevitable adverse effects and increased incidence of drug reduction, it is concerning that clinical research focusing on the initial dose and response rate might not accurately reflect survival.

In the present study, the initial dose of lenvatinib was 24 mg in 81% of the patients (n=34), and our results indicate that the initial dose of lenvatinib does not make a significant difference in the patients' survival (data not shown). The group with an average dose ranging from 4.56 to 7.97 mg demonstrated the most favorable outcomes. Minimizing adverse events is crucial for long-term treatment with lenvatinib, and while a patient's blood pressure elevation can be controlled with antihypertensive drugs, proteinuria, renal dysfunction, and hand-foot syndrome have no solutions other than lenvatinib discontinuation. A moderate dose reduction and drug holidays are thus considered necessary for longer treatment periods. We do not intend to recommend "fundamentally" decreasing a patient's starting dose of lenvatinib. Even if the initial dose has been set as 24 mg following the standard protocol for lenvatinib treatment, it might not be necessary to persist with that dose, depending on the condition of the

Table 3 Multivariate analysis – COX Proportional-Hazards Model

Overall Survival (N = 42)

		Case*/Total number (%)	Model 1 †			Model 2 ‡			Model 3 $			Model 3 #		
			HR	(95% CI)	*P*-value	HR	(95% CI)	*P*-value	HR	(95% CI)	*P*-value	HR	(95% CI)	*P*-value
mean dose														
Q1	1.14–4.54 mg	2/14 (14.3)	**0.11**	**(0.02–0.78)**	**0.027**	0.38	(0.03–4.99)	0.461	**0.12**	**(0.02–0.92)**	**0.041**	0.26	(0.02–3.81)	0.327
Q2	4.56–7.97 mg	4/14 (28.6)	**0.06**	**(0.01–0.37)**	**0.002**	**0.01**	**(0.00–0.13)**	**0.000**	**0.06**	**(0.01–0.70)**	**0.024**	**0.03**	**(0.003–0.30)**	**0.003**
Q3	8–24 mg	9/14 (64.3)	1	reference		1	reference		1	reference		1	reference	
drug interruption														
Q1	0–24.84%	5/14 (35.7)				1	reference					1	reference	
Q2	24.90–39.13%	8/14 (57.1)				2.31	(0.45–12.00)	0.318				0.82	(0.14–4.83)	0.823
Q3	41.17–92.58%	2/14 (14.3)				0.08	(0.00–1.34)	0.080				**0.003**	**(0.000–0.23)**	**0.009**
cumulative dose														
Q1	81–1,140 mg	6/14 (42.9)							1	reference		1	reference	
Q2	1,194–3,028 mg	5/14 (35.7)							1.35	(0.19–9.53)	0.763	**0.03**	**(0.001–0.89)**	**0.043**
Q3	3,066–12,434 mg	4/14 (28.6)							0.82	(0.09–7.60)	0.861	**0.02**	**(0.001–0.74)**	**0.033**

Progression Free Survival (N = 42)

		Case*/Total number (%)	Model 1 †			Model 2 ‡			Model 3 $			Model 3 #		
			HR	(95% CI)	*P*-value	HR	(95% CI)	*P*-value	HR	(95% CI)	*P*-value	HR	(95% CI)	*P*-value
mean dose														
Q1	1.14–4.54 mg	7/14 (50)	0.56	(0.10–3.15)	0.514	0.48	(0.07–3.33)	0.459	0.34	(0.05–2.30)	0.270	0.36	(0.05–2.66)	0.319
Q2	4.56–7.97 mg	7/14 (50)	**0.07**	**(0.01–0.38)**	**0.002**	**0.07**	**(0.01–0.40)**	**0.002**	**0.13**	**(0.02–0.78)**	**0.026**	**0.13**	**(0.02–0.83)**	**0.031**
Q3	8–24 mg	9/14 (64.3)	1	reference		1	reference		1	reference		1	reference	
drug interruption														
Q1	0–24.84%	7/14 (50)				1	reference					1	reference	
Q2	24.90–39.13%	9/14 (64.3)				1.42	(0.40–5.04)	0.592				1.01	(0.25–4.09)	0.985
Q3	41.17–92.58%	7/14 (50)				1.33	(0.28–6.36)	0.720				0.844	(0.14–5.26)	0.856
cumulative dose														
Q1	81–1,140 mg	6/14 (42.9)							1	reference		1	reference	
Q2	1,194–3,028 mg	5/14 (35.7)							0.66	(0.13–3.49)	0.629	0.62	(0.10–3.78)	0.604
Q3	3,066–12,434 mg	4/14 (28.6)							0.34	(0.05–2.31)	0.272	0.31	(0.03–2.89)	0.307

CI, confidence interval; HR, harzard ratio.

*Case: number of cases those experienced events such as death and/or disease progression

† Adjusted factors: age, sex, PS, side effects (hand-foot syndrome, hypertension, proteinuria)

‡ Adjusted factors: Model 1 + drug interruption

$ Adjusted factors: Model 1 + cumulative dose

Adjusted factors: Model 2 + cumulative dose

individual patient.

The study limitations include the following. This was a retrospective analysis of only 42 patients treated at a single center, and this posed challenges in the simultaneous analysis of several prognostic factors. Selection bias of the patients could not be eliminated. In addition, no guideline or criterion for the estimation of the daily dose or period of interruption for lenvatinib treatment was available, and the decisions regarding the treatment were made at the discretion of attending physicians based on the patient's condition.

In conclusion, lenvatinib is effective at relatively low daily doses despite long intervals of drug interruption for the treatment of Japanese patients with unresectable thyroid carcinoma. A continuation of lenvatinib treatment with an adequate daily dose and the establishment of an appropriate interruption period considering its effect and burden on patients are important. Since 4-mg and 10-mg lenvatinib capsules are available, a low daily dose of 8 mg or 10 mg might be an ideal medication as a maintenance dose, and it might not be necessary to persist with the standard 24-mg starting dose, depending on the patient's condition.

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