Low-Dose Continuation of Lenvatinib for the Treatment of the Patients with Unresectable Thyroid Carcinoma

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Research Article

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Abstract

Background

Lenvatinib, a multi-tyrosine kinase inhibitor (TKI), has been proven to be an effective treatment option for patients with unresectable thyroid carcinoma. However, it causes certain adverse effects (AEs), and discontinuation or dose reduction of the drug is almost unavoidable. Few studies have investigated the impact of the length, dose, or interruption of lenvatinib administration on the prognosis of patients with unresectable thyroid carcinoma. Here, we aimed to verify the significance of our efforts to continue lenvatinib therapy to the longest duration possible with a reasonable daily dose and minimum discontinuation period in patients with unresectable thyroid carcinoma.

Methods

The clinical records of 42 patients with unresectable thyroid carcinoma treated with lenvatinib between 2015 and 2020 were retrospectively studied.

Results

The Cox proportional hazard model-based analysis indicated that the overall survival (OS) of patients treated with a mean dose of lenvatinib <8 mg/day was significantly better than that of those treated with 8-24 mg/day (hazard ratio (HR)=0.38, 95% confidence interval (CI): 0.03-4.99 for 1.14-4.54 mg/day, and HR=0.01, 95% CI: 0.00-0.13 for 4.56-7.97 mg/day) adjusted for various factors (sex, age, length of drug interruption, and so on). The cumulative administration dose of lenvatinib tended to be higher in patients treated with low doses (<8 mg/day) than in those treated with relatively high doses (8-24 mg/day).

Conclusion

Considering its AEs, continuation of lenvatinib administration with an adequate daily dose with drug interruption may be important for prolonging survival of patients with unresectable thyroid carcinoma.

Introduction

The phase Ⅲ Study of Lenvatinib in Differentiated Cancer of the Thyroid (SELECT) proved that treatment with lenvatinib—an oral, multitargeted tyrosine kinase inhibitor (TKI)—prolonged progression-free survival (PFS) in patients with radioactive iodine (RAI)-refractory differentiated thyroid carcinoma. Furthermore, 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 patients (n=261) and 100% of the Japanese patients (n=30) treated with lenvatinib presented with a few adverse effects (AEs), such as hypertension, diarrhea, loss of appetite, proteinuria, or hand-foot syndrome [1]. Specifically, older age and poorer performance status (PS) of patients can cause higher toxicity of lenvatinib [5]. Although the recommended dose of lenvatinib was established as 24 mg once daily, most patients in daily clinical practice cannot continue treatment with the drug at the starting dose, mostly due to the occurrence of diarrhea, hypertension, or proteinuria [6]. A study reported that frequency of hypertension induced by lenvatinib increased especially in elderly patients aged 75 years or older, and early blood pressure control might be an effective approach to maintain the lenvatinib dose intensity [7]. The flare phenomenon was defined as death, hospitalization attributable to tumor progression, or an unexpected event (e.g., pleural drainage) within 1 month of lenvatinib cessation, and the overall survival (OS) tended to be poorer in the flare group than that in the non-flare group [8]. The incidence of flare phenomenon 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 a reasonable but maximum dose of lenvatinib with minimum discontinuation 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 therapy as well as alternative therapeutic approaches including best supportive care” [9].

In the present study, we verified the significance of our efforts to continue lenvatinib therapy to the longest duration possible with a reasonable daily dose and minimum discontinuation period in patients with unresectable thyroid carcinoma.

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), 3 with follicular thyroid carcinoma (FTC), and 4 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 shown in Table 1. The 42 patients comprised 17 men (40.5%) and 25 women (59.5%). The mean age at the initiation of lenvatinib therapy was 71 years (range, 43-91 years). The PS was “0” in 27 patients, “1” in 10 patients, and “2” in 5 patients. The mean body mass index (BMI) was 22.0 (range, 15.2-32.1). A total of 29 (69.0%) patients had undergone RAI therapy. Furthermore, 5 (11.9%) patients 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 7 (18.9%) patients, at least one lesion was found to be in contact with a major artery. In such patients, lenvatinib was used after providing explanation to and discussion with the patients and their family members, and after the conduction of frequent imaging studies. The mean duration of follow-up for surviving patients after the commencement of lenvatinib therapy was 592 days (range, 23-1736 days).

Table 1
Clinical characteristics

	Total		daily dose tertiles						*p-value*
			Q1: 1.14~4.54mg		Q2: 4.56~7.97mg		Q3: 8~24mg		
	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 (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)	2371 (81-12434)		2371 (81-5474)		2977 (476-11510)		1326 (188-12434)		*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*

Considering the condition of each patient, the starting dose of the lenvatinib was 24 mg in 34 patients, 20 mg in 1 patient, 14 mg in 5 patients, and 10 mg in 2 patients, and 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, # tracheal invasion, # untreated hypertension, # advanced age (>85years), and #PS. Prognostic factors evaluated in the current study 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, average daily dose, total administration dose, frequency and period of discontinuation, ratio of total discontinuation period to total therapeutic period, and AEs. AEs were evaluated using the Common Terminology Criteria for AEs (CTCAE), version 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 number 2338) and conformed to the amended Declaration of Helsinki. The need for informed consent was waived in accordance with the Committee's instruction, because of the retrospective nature of the study design. The study information was presented on the Web for the opportunity to opt out from this research, which was substituted for the participants' consent.

Statistical analyses

We checked medication status and adherence in each medical consultation. From the administered dose, total treatment period (days) and number of days of drug suspension, we calculated cumulative dose, rate of drug interruption and mean dose per day (total treatment period into cumulative dose). The mean dose was categorized 42 patients with unresectable thyroid carcinoma into daily dose tertiles (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). Furthermore, the rest period (i.e., the proportion of the period when lenvatinib treatment was tentatively halted to the entire treatment period) was categorized into tertiles: Q1 (0-24.84%), Q2 (24.90-39.13%), and Q3 (41.17-92.58%).

First, we described demographic and clinical characteristics both in total and stratified by daily dose tertiles (Q1-Q3). We performed one-way analysis of variance to compare the average age and BMI and Pearson's chi-square test to compare categorical variables among groups. Second, we used Kaplan-Meier survival curves to demonstrate both OS and PFS, which were calculated from the time of initiation of lenvatinib treatment. The log-rank test and the generalized Wilcoxon test were used to determine significant differences in survival. Values were considered statistically significant at 2-sided P <0.05. Third, we used the Cox proportional hazard model to perform adjustments for possible confounding factors. In model 1, we adjusted for age, sex, PS (0/1-2), and side effects (hand-foot syndrome, hypertension, and proteinuria), and 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. Lastly, we restricted the adjusted analyses to only differentiated carcinoma (n=38). All analyses were performed using JMP 15 (SAS Institute Inc., Cary, NC, USA) and Stata/SE 16.1 (StataCorp, College Station, TX, USA).

Results

Of the 42 patients with unresectable thyroid carcinoma treated with lenvatinib, 16 (38.1%) succumbed to the disease during the observation period. 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), version 1.1, 2 (4.9%) patients achieved partial response (PR), 38 (92.7%) patients presented with stable disease (SD), 1 (2.4%) patient presented with progressive disease (PD), and 1 patient was categorized as N/A. No patient achieved complete response (CR). The median OS after the commencement of lenvatinib therapy was 1265 days (range, 23-1736 days; without ATC (n=4), 1399 days) (Fig. 1 (a)), and median PFS was 855 days (range, 15-1582 days; without ATC, 765 days) (Fig. 1 (b)). The median therapeutic period was 728 days (without ATC, 1015 days). Twenty-nine (69.0%) of the forty-two patients discontinued lenvatinib therapy due to various reasons; 13 patients discontinued lenvatinib therapy due to disease progression, 11 patients discontinued due to the development of serious AEs (renal dysfunction/proteinuria in 5, pneumonia in 1, minor bleeding in 1, drug eruption in 1, hypertension along with risk of bleeding in 1, palpitation in 1, thrombocytopenia in 1), 1 patient discontinued due to leukemia, 2 patients discontinued due to other reasons such as economic burden and difficulty in attending hospitals, and 2 cases were lost to follow-up (Table 2). Contact with major arteries, which was one of the reasons to reduce initial dose, did not cause drug interruption or termination (Figure 2 and Table 2). The median value of 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 2371 mg (range, 81-12434 mg). The average frequency of therapy interruption was 14.0 times (range, 0-108) and each interruption period spanned for 20.6 days (range, 0-112 days) on average. The most frequent reasons for therapy interruption for the first to third times were hypertension, followed by renal dysfunction/proteinuria, hand-foot syndrome, general fatigue, or thrombocytopenia. Hypertension was the most frequently observed each time; 1st 38.1%, 2nd 25.6%, 3rd 25.0% (Fig. 2). The average ratio of total discontinuation period to total therapeutic period was 34.3% (range, 0-92.6%).

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	

Among the various prognostic factors, the patients with PS1 or PS2 were 53 times more likely to succumb than those with PS0 at a given time point after the treatment, assuming that they survived for a specific time; furthermore, the cumulative dose of lenvatinib tended to be higher in the patients who received a smaller daily dose (Q1 and Q2 in the Table 1) than those who received a larger daily dose; Median cumulative doses were 2371mg in mean dose Q1(1.14-4.54 mg/day), 2977mg in Q2 (4.56-7.97 mg/day) and 1326mg in Q3 (8.00-24 mg/day). With exclusion of 5 outlier cases (one case with mean dose of 24mg and 4

cases with cumulative dose exceeded 8000mg), negative correlation between cumulative dose and mean dose was observed (r=-0.1362). Among the patients categorized into tertiles based on different average dose per day, both OS and PFS of Q1 (1.14-4.54 mg/day) and Q2 (4.56-7.97 mg/day) were significantly better than those of Q3 (8.00-24 mg/day) (Fig. 3 (a), (b)), and the results remain unaltered even when values were statistically adjusted for various factors (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 OS; and 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 for PFS). Drug interruption did not tend to have effect on survival (Table 3).

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)	
mean dose														
Q1	1.14~4.54mg	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)	
Q2	4.56~7.97mg	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)**	
Q3	8~24mg	9/14(64.3)	1	reference		1	reference		1	reference		1	referenc	
drug interruption														
Q1	0~24.84%	5/14(35.7)				1	reference					1	referenc	
Q2	24.90~39.13%	8/14(57.1)				2.31	(0.45-12.00)	0.318				0.82	(0.14-4.83)	
Q3	41.17~92.58%	2/14(14.3)				0.08	(0.00-1.34)	0.080				**0.003**	**(0.000-0.23)**	
cumulative dose														
Q1	81~1140mg	6/14(42.9)							1	reference		1	referenc	
Q2	1194~3028mg	5/14(35.7)							1.35	(0.19-9.53)	0.763	**0.03**	**(0.001-0.89)**	
Q3	3066~12434mg	4/14(28.6)							0.82	(0.09-7.60)	0.861	**0.02**	**(0.001-0.74)**	
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)	
mean dose														
Q1	1.14~4.54mg	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)	
Q2	4.56~7.97mg	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)**	
Q3	8~24mg	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)	
Q3	41.17~92.58%	7/14(50)				1.33	(0.28-6.36)	0.720				0.844	(0.14-5.26)	
cumulative dose														
Q1	81~1140mg	6/14(42.9)							1	reference		1	reference	
Q2	1194~3028mg	5/14(35.7)							0.66	(0.13-3.49)	0.629	0.62	(0.10-3.78)	
Q3	3066~12434mg	4/14(28.6)							0.34	(0.05-2.31)	0.272	0.31	(0.03-2.89)	

Abbreviations: CI: confidence interval, HR: harzard ratio

† 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

Furthermore, based on the analysis of these data excluding 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 AEs are more likely to opt for interruption or cessation of lenvatinib treatment [10], a few patients discontinued the treatment because of the economic burden and challenges involved in visiting hospitals. Compared with placebo or best supportive care, lenvatinib costs more than £50,000 per quality-adjusted life-years (QALY) gained, whereas a cost-effectiveness threshold range between £20,000 and 30,000 per QALY [11]. Moreover, even in Japan where a national health insurance program has been established, it is important for the treatment benefits to overcome both the economic and somatic burden of patients to ensure continuation of lenvatinib treatment.

Low-dose administration of lenvatinib will ease both the economic and somatic burden of patients; moreover, the present study demonstrated that low-dose lenvatinib might be effective at least for Japanese patients, with daily low-dose administration resulting in prolonged OS of the patients. Lenvatinib-emergent hypertension was significantly correlated with improved clinical outcomes [12], and the OS benefit was 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 patients. In addition, more than 20% of those hypertensive patients presented with hypertension within 2 weeks after starting lenvatinib therapy [1]. Since hypertension was the most frequently observed AE resulting in drug interruption, low-dose administration of lenvatinib may be effective for the patients in whom reduction of the daily dose of lenvatinib is necessary owing to the occurrence of AEs. A study reported from Korea showed that treatment with a sustainable dose of lenvatinib 10 mg/day helped achieve tumor shrinkage in 90.7% and PR in 64.7% of the total 43 patients [13]. The standard protocol for lenvatinib treatment is based on data obtained from Western populations; thus, dose adjustment may be necessary for Asian populations because of their smaller physique [13]. In this study, initial dose of lenvatinib was 24mg in the 34 cases (81%). On the other hands, there have been some papers comparing full initial dose (24mg) of lenvatinib and lower initial dose, which concluded that lower initial dose does not deteriorate survival [14]. Our results indicated that initial dose of lenvatinib did not make significant difference in survival as well (data not shown). We do not intend to recommend “fundamentally” decrease the starting dose, but it might not be necessary to persist in the starting dose 24mg considering the condition of an individual patient.

The study limitations include the following: first, the current retrospective study reported from a single center included only 42 patients; this posed challenges in the analysis of several prognostic factors simultaneously. Second, selection bias of the patients could not be eliminated. Third, no guideline or criterion for the estimation of the daily dose or period of interruption for lenvatinib administration was available, and the decisions were at the discretion of attending physicians based on the patient’s condition.

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

Declarations

Conflict of Interest Disclosure Statement: All authors have completed the “Conflict of Interest Disclosure Statement” and declare that: (i) no support, financial or otherwise, has been received from any organization that may have an interest in the submitted work; and (ii) there are no other relationships or activities that could appear to have influenced the submitted work.

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Conflict of interest: None.

Ethical approval: The study was approved by Bioethics Committee of Kumamoto University (approval number 2338; project title: Retrospective clinical study about head and neck tumors).

Author contribution: All authors contributed to the study conception and design. Data collection and analysis were performed by Kohei Nishimoto, Soshi Takao and Tomoka Kadowaki. The first draft of the manuscript was written by Daizo Murakami and Yorihisa Orita. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

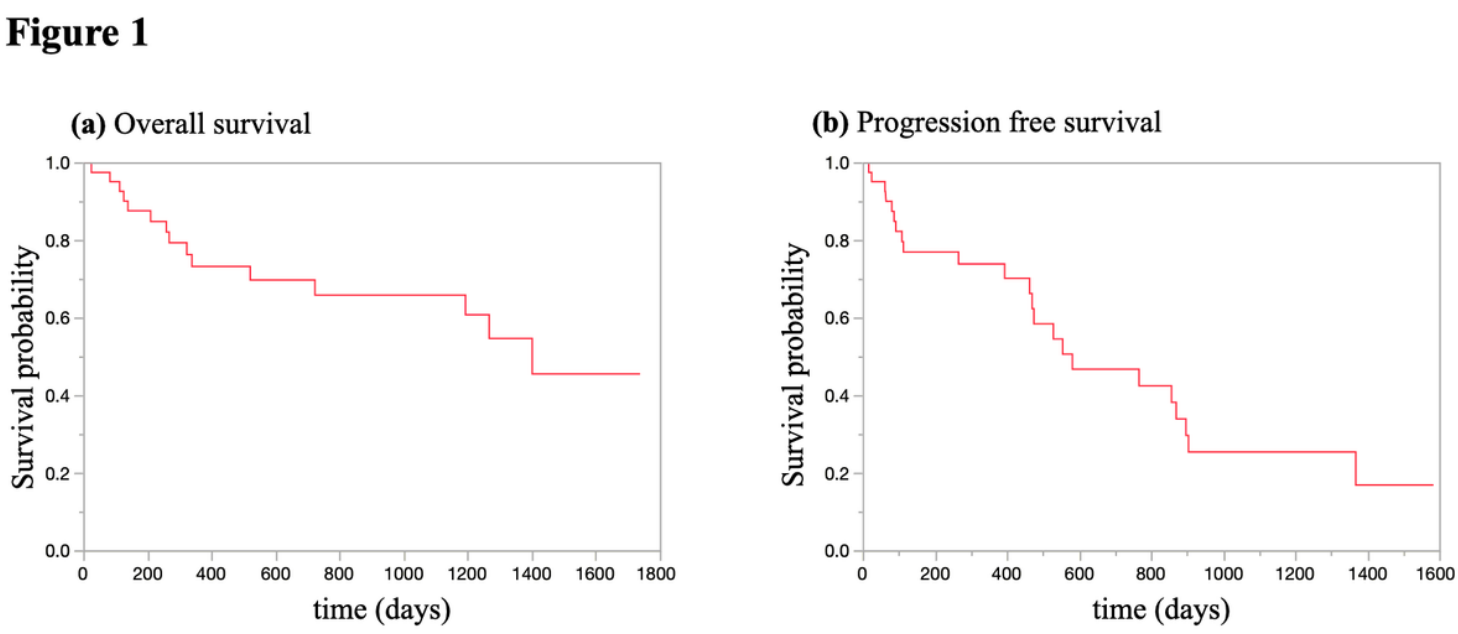

Figure 1

Kaplan-Meier analysis of (a) overall survival and (b) progression-free survival of the total population

Figure 2

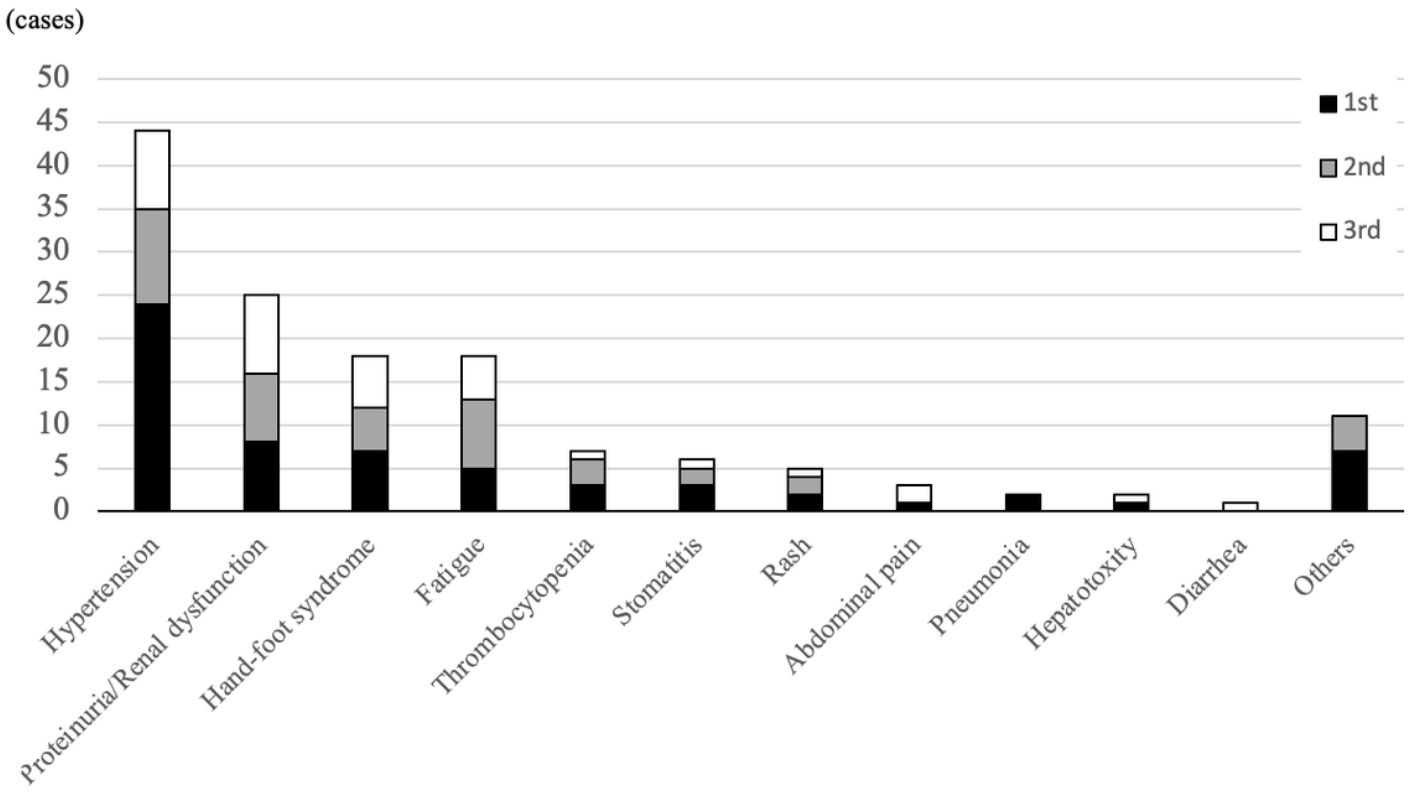

Figure 2

Reasons for therapy interruption for the first to third times

Figure 3

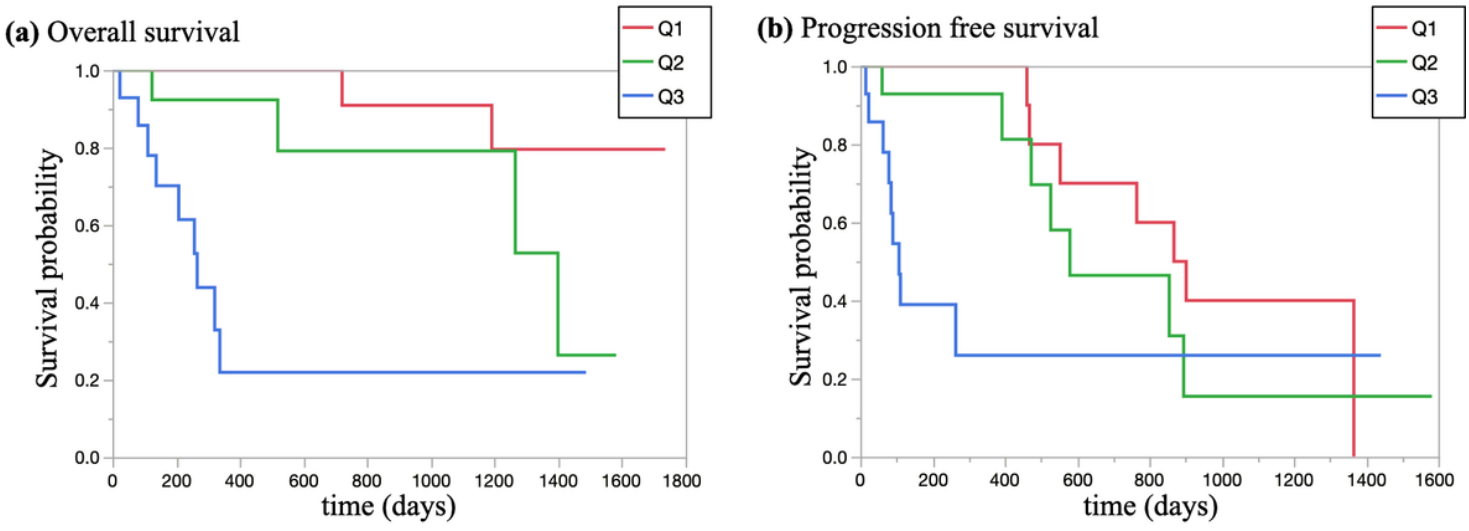

Figure 3

Kaplan-Meier analysis of (a) overall survival and (b) progression-free survival by tertiles (Q1-Q3) based on average daily dose of lenvatinib