

Associations Between Plasma Concentrations of Lenvatinib and Angiopoietin and Clinical Responses to Lenvatinib Therapy in Japanese Patients With Thyroid Cancer

MAHO KUMAGAI¹, MITSUJI NAGAHAMA², YUMIKO AKAMINE¹, TOMOKO OZEKI¹, AKIFUMI SUZUKI², KIMINORI SUGINO², KOICHI ITO² and MASATOMO MIURA^{1,3}

¹Department of Pharmacy, Akita University Hospital, Akita, Japan;

²Department of Surgery, Ito Hospital, Tokyo, Japan;

³Department of Pharmacokinetics, Akita University Graduate School of Medicine, Akita, Japan

Abstract. *Background/Aim:* The purpose of this study was to investigate the relationships between the plasma concentration of Lenvatinib (C_0), the levels of angiopoietin (Ang)-1 and Ang-2, and clinical responses to lenvatinib therapy in patients with thyroid cancer. *Patients and Methods:* Lenvatinib C_0 and Ang were measured by high-performance liquid chromatography and enzyme-linked immunosorbent assay, respectively. *Results:* The median decrease rates of Ang-1 and Ang-2 at 1 month after treatment from baseline were -15.3% and -48.4% , respectively. However, the decrease in the levels of Ang-1 and Ang-2 at 1 month from baseline did not correlate with C_0 . In patients with partial response (PR) and stable disease, Ang-2 at 1 month was significantly lower than Ang-2 at baseline. The area under the ROC for PR prediction was 0.667, giving the best sensitivity (69.2%) and specificity (73.9%) at a threshold of decrease rate of Ang-2 of -49.83% . *Conclusion:* The decrease in Ang-2 at 1 month of treatment from baseline may be important as a biomarker of the inhibitory effect of lenvatinib on angiogenesis.

Correspondence to: Masatomo Miura, Ph.D., Department of Pharmacokinetics, Akita University Graduate School of Medicine, 1-1-1 Hondo, Akita 010-8543, Japan. Tel: +81 188846310, Fax: +81 188362628, e-mail: m-miura@hos.akita-u.ac.jp

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Lenvatinib is an oral inhibitor of multiple tyrosine kinase receptors, including vascular endothelial growth factor (VEGF) receptors 1-3, fibroblast growth factor receptors 1-4, platelet-derived growth factor receptor alpha, stem cell factor receptor, and rearranged during transfection (1-4), and it is approved for the treatment of thyroid cancer. VEGF receptors 1-3 are expressed on endothelial cells and play important roles in both physiologic and pathologic angiogenesis (5), and the angiogenesis induced by over-expression of VEGF has been reported to be significantly suppressed by treatment with lenvatinib (4).

Angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2) are ligands of the endothelial-specific receptor tyrosine kinase Tie2 (6). VEGF and Ang-2 are expressed early in tumor formation, and their levels increase throughout tumor growth (7). Ang-2 facilitates VEGF-induced angiogenesis and is expressed during vascular remodeling (8). On the other hand, changes in the expression of Tie2 and Ang-1 are not observed throughout tumor growth (7). Previously, baseline levels of Ang-2 prior to lenvatinib therapy in patients with advanced medullary or differentiated thyroid cancer have been reported to be predictive of the clinical outcomes of lenvatinib (9, 10). Namely, low baseline levels of Ang-2 before lenvatinib therapy are associated with tumor reduction and prolonged progression-free survival (PFS) (9, 10). Therefore, Ang-2 may be predictive of the sensitivity to lenvatinib.

Relationships between plasma concentrations and efficacy or toxicity of oral targeted antineoplastic drugs have been studied intensely (11, 12). The target plasma trough concentration (C_0) of lenvatinib in patients with thyroid cancer is approximately 51.5 ng/ml based on the mean C_0 at the steady-state as has been shown in a phase 3 trial (11). In our previous study, we demonstrated that the target lenvatinib C_0 , as the threshold between the C_0 and optimal response, lies

within the range from 42 to 88 ng/ml (13). Therefore, Ang-2 levels are reduced as part of the inhibitory effect of lenvatinib on angiogenesis, and plasma concentration of lenvatinib may relate to the decreasing levels of Ang-2 from baseline. However, the association between plasma concentration of lenvatinib and Ang-2 have not yet been clarified.

Therefore, in the present study, we aimed to retrospectively examine the relationship between plasma concentration of lenvatinib and Ang-2, and the impact of these concentrations on clinical responses to lenvatinib therapy in Japanese patients with thyroid cancer.

Patients and Methods

Patients and protocols. Thirty-seven Japanese patients who received treatment with lenvatinib (LENVIMA; Eisai Co., Ltd., Tokyo, Japan) for thyroid cancer at Ito Hospital from January 2016 through December 2018 were consecutively enrolled in this study. One female patient was excluded because of adverse events that occurred shortly after beginning treatment with 24 mg/day lenvatinib. Accordingly, thirty-six patients (23 women and 13 men) were analyzed in this study. Thirty-four patients in this study had participated in our previous studies (13). The mean age was 65 ± 11 years, and the mean body weight was 59 ± 14 kg. There were no patients with serious renal or hepatic dysfunction. The study was approved by the Ethics Committees of Ito Hospital (approval numbers 137 and 330) and Akita University School of Medicine (approval number 790) and 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.

The inclusion criteria were in accordance with the standard eligibility criteria for lenvatinib treatment (14). 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 evaluation of clinical response was determined by computed tomography according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria at 1 month after the beginning of lenvatinib treatment, and then every 3 months during the first year and every 3 to 6 months during the following 3 years, depending on the response to treatment and clinical condition of the patient. The overall survival (OS) was defined as the time from first lenvatinib administration until death from any cause or until the final follow-up.

At 1 month (range from day 22 to day 36 after administration) and 1 year after lenvatinib therapy, whole blood samples (5 ml) were collected by venepuncture just before administration (C_0) of lenvatinib. Plasma was isolated by centrifugation at $1,900 \times g$ for 15 min and stored at -40°C until analysis. Quantifications of lenvatinib C_0 , Ang-1 and Ang-2 in plasma were performed at the same time. Ang-1 and Ang-2 levels at baseline were analyzed via blood sampling within 1 week before the initiation of lenvatinib therapy.

Analytical methods. Lenvatinib C_0 was measured by high-performance liquid chromatography (HPLC) and ultraviolet spectroscopic analysis, as previously described (13, 15). The calibration curve generated for lenvatinib in human plasma was linear over the concentration range of 5 to 1,000 ng/ml. The limit of quantification of lenvatinib for this assay was 5 ng/ml. The

coefficients of variation and accuracies for intra- and inter-day assays at the concentration range of 5 to 1,000 ng/ml were less than 12.6% and within 10.6%, respectively. Plasma concentrations of Ang-1 and Ang-2 were assayed using enzyme-linked immunosorbent assays (ELISA) (R&D Systems Inc., Minneapolis, MN, USA), following the manufacturer's instructions.

Statistical analyses. Shapiro–Wilk tests were used to assess distributions. Spearman's rank correlation coefficient values were used to assess correlations between continuous values. 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 comparisons between two groups after comparisons among three groups. Receiver operating characteristic (ROC) curves were used to determine the best cut-off values for predictive factors. Survival curve for overall survival (OS) was analyzed using the Kaplan–Meier method. Statistical analyses were performed with SPSS 20.0 for Windows (SPSS IBM Japan Inc., Tokyo, Japan).

Results

Median Ang-1 and Ang-2 levels at 1 month after initiation of treatment of 36 patients with lenvatinib were significantly lower than those pre-therapy (Ang-1: 5,750 pg/ml from 6,459 pg/ml, $p < 0.001$; Ang-2: 967 pg/ml from 1,590 pg/ml, $p < 0.001$). The median rates of decrease in Ang-1 and Ang-2 levels at 1 month from baseline were -15.3% and -48.4% , respectively. However, these rates did not correlate with the C_0 for lenvatinib at 1 month after initiation of treatment (Figure 1). However, there were no significant differences in Ang-1 or Ang-2 levels between the 1 month and 1 year time points ($p = 0.267$ and 0.248 , respectively).

Partial response (PR), stable disease (SD) and progressive disease (PD) were observed following lenvatinib treatment in 23, 8, and 5 patients, respectively (Table I). Among PR, SD, and PD groups, there were no significant differences in Ang-1 plasma levels at baseline or at 1 month and 1 year after initiation of lenvatinib therapy, and there were no significant differences in the rate of decrease in Ang-1 at 1 month and 1 year from baseline (Table I). However, in patients with PR to lenvatinib, Ang-1 levels 1 month after treatment initiation were significantly lower than Ang-1 levels at baseline ($p < 0.01$, Table I).

Similar to the Ang-1 levels, there were no significant differences in Ang-2 levels at baseline or at 1 month and 1 year after initiation of lenvatinib therapy among patients with PR, SD and PD; however, in patients with PR to lenvatinib, Ang-2 levels at 1 month and 1 year after treatment initiation were significantly lower than Ang-2 levels at baseline ($p < 0.001$ and $p < 0.01$, respectively, Table I).

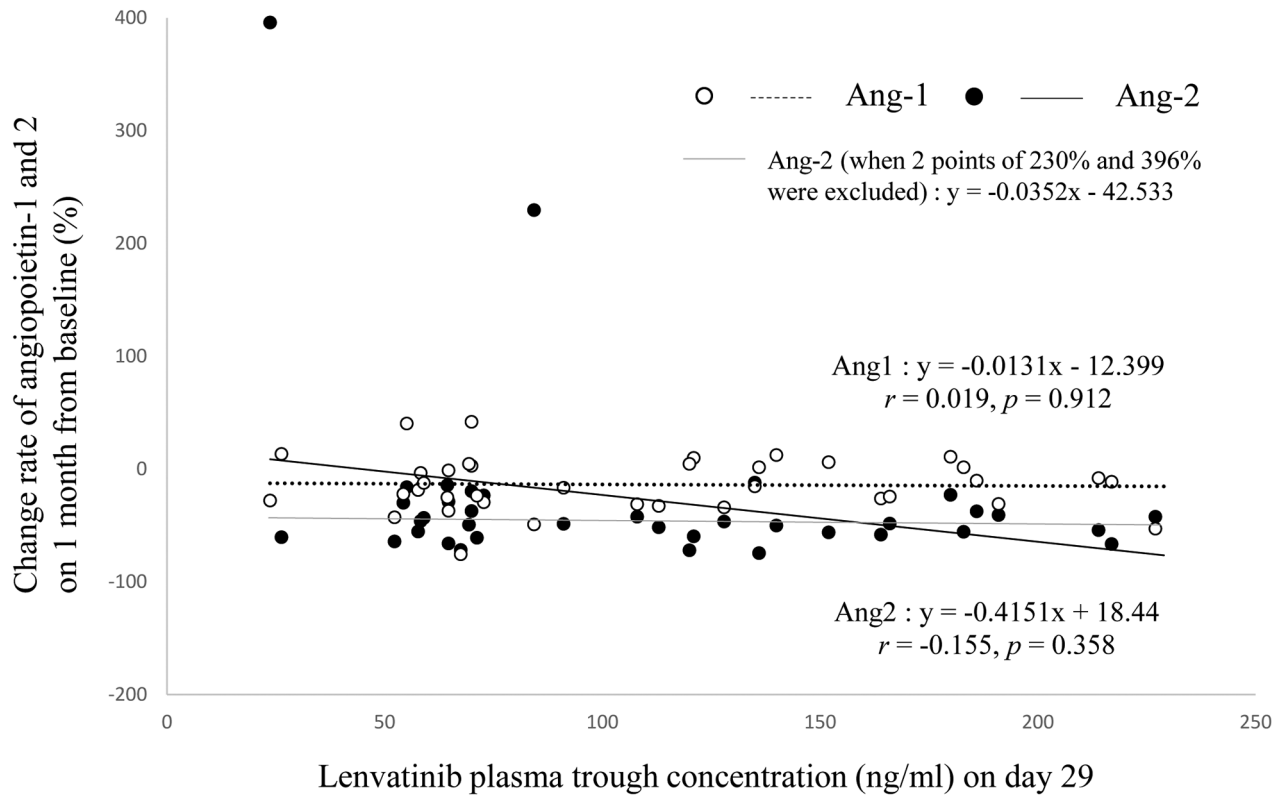


Figure 1. Relationship between rate of change of angiopoietin-1 (open circles) and angiopoietin-2 (closed circles) at 1 month after initiation of lenvatinib treatment from baseline with trough plasma concentrations of lenvatinib at 1 month.

There were no significant differences in lenvatinib C_0 1 month after treatment initiation among patients with PR, SD and PD (Table I); however, in patients with PR, lenvatinib C_0 at 1 year after treatment initiation was significantly lower than that at 1 month ($p < 0.01$).

A waterfall plot of rate of decrease in Ang-2 levels 1 month after initiation of lenvatinib therapy relative to baseline is shown in Figure 2. The rate of decrease in Ang-2 levels in 2 patients (1 patient with papillary thyroid cancer and 1 patient with follicular thyroid cancer) increased after lenvatinib therapy, and these 2 patients showed PD following lenvatinib therapy.

A ROC analysis showed the discrimination potential of the rate of decrease in Ang-2 levels for prediction of PR to lenvatinib (Figure 3). The area under the ROC was 0.667 [95% confidence interval (CI)=0.478-0.873], giving the best sensitivity (69.2%) and specificity (73.9%) at a threshold of the rate of decrease in Ang-2 levels of -49.83% .

Patients were divided into two groups depending on their exhibited rates of decrease in Ang-2 levels: those with rates of decrease at least -49.83% and those with rates of decrease less than -49.83% . The OS rates of patients in the group

with a decrease of at least -49.83% tend to be longer than those with a decrease less than -49.83% , but these differences were not statistically significant (median OS: 676 days and 273 days, respectively, Figure 4). The median 1-year OS of patients having rates of decrease in the levels of Ang-2 of at least -49.83% and less than -49.83% were 62.5% and 45%, respectively.

Furthermore, the 18 patients that continued treatment with lenvatinib for 1 year were compared with 18 patients who discontinued treatment at less than 1 year (Table II). There were no significant differences between Ang-1 and Ang-2 levels at baseline or at 1 month after initiation of lenvatinib therapy. The rates of decrease in Ang-1 and Ang-2 levels at 1 month relative to baseline between these 2 groups were also not significantly different. In addition, there was no significant difference in lenvatinib C_0 at 1 month after initiation of treatment between these 2 groups (Table II).

However, in patients who continued lenvatinib treatment beyond 1 year, Ang-2 levels and the Ang-2/Ang-1 ratio at 1 month and 1 year after treatment initiation were significantly lower than those at baseline (each $p < 0.001$, Table II). In addition, lenvatinib C_0 at 1 year after treatment initiation was

Table I. Association between plasma concentration of angiotensin-converting enzyme 1, -2 and lenvatinib and clinical response after lenvatinib therapy.

Best response	Partial response		Stable disease		Progressive disease		p-Value
Number	23	8	5				
	Median	(Q1-Q3)	Median	(Q1-Q3)	Median	(Q1-Q3)	
Age	68	(61-71)	62.5	(51.8-75.8)	71	(58-75.5)	0.733
Female:Male	14:9		5:3		4:1		0.747
PTC/FTC/MTC/PDTC/ATC	9/4/1/4/5		3/3/0/0/2		1/1/0/0/3		0.708
Angiotensin-converting enzyme 1							
Before lenvatinib therapy (baseline) (pg/ml)	6,667	(4,833-8,083)	6,083	(4,653-8,146)	6,833	(5,334-8,500)	0.739
1 month after lenvatinib treatment (pg/ml)	5,417	(3,833-6,333)**	6,250	(5,349-7,145)	5,750	(3,792-6,500)	0.395
1 year after lenvatinib treatment (pg/ml)	5,542	(4,490-7,188)	7,250	(4,792-8,395)			0.442
Change on 1 month from baseline (%)	-16.7	(-29.3-1.6)	-2.9	(-19.3-33.5)	-28.0	(-40.2-4.6)	0.192
Change on 1 year from baseline (%)	4.1	(-18.1-20.4)	2.0	(-15.2-31.0)			0.878
Angiotensin-converting enzyme 2							
Before lenvatinib therapy (baseline) (pg/ml)	1,773	(1,343-2,918)	1,570	(1,472-1,928)	2,136	(1,080-2,887)	0.770
1 month after lenvatinib treatment (pg/ml)	1,005	(651-1,517)***	893	(790-1,007)*	936	(780-11,408)	0.632
1 year after lenvatinib treatment (pg/ml)	1,046	(851-1,460)**	1,015	(936-1,387)			0.878
Change on 1 month from baseline (%)	-51.8	(-60.5- -40.7)	-39.8	(-62.4- -31.9)	-12.1	(-49.2-313)	0.081
Change on 1 year from baseline (%)	-40.2	(-59.3- -29.1)	-36.9	(-47.3- -11.6)			0.442
Angiotensin-converting enzyme 2/angiotensin-converting enzyme 1 ratio							
Before lenvatinib therapy (baseline)	0.31	(0.20-0.51)	0.25	(0.21-0.32)	0.33	(0.13-0.53)	0.625
1 month after lenvatinib treatment	0.17	(0.13-0.35)***	0.15	(0.13-0.20)*	0.16	(0.12-3.31)	0.625
1 year after lenvatinib treatment	0.20	(0.14-0.28)**	0.17	(0.13-0.21)			0.442
Lenvatinib							
C ₀ on 1 month after lenvatinib treatment (ng/ml)	71.2	(64.4-164)	130	(58.8-209)	108	(54.0-144)	0.598
C ₀ on 1 year after lenvatinib treatment (ng/ml)	49.7	(37.0-113)##	77.2	(30.7-138)			0.721
Daily dose on 1 month after lenvatinib treatment (mg)	20.0	(20.0-24.0)	24.0	(16.5-24.0)	14.0	(12.0-22.0)	0.119
Daily dose on 1 year after lenvatinib treatment (mg)	10.0	(9.5-14.5)##	11.0	(8.0-14.0)			0.721

Q: Quartile; PTC: Papillary thyroid cancer; FTC: follicular thyroid cancer; MTC: medullary thyroid cancer; PDTC: poorly differentiated thyroid cancer; ATC: anaplastic thyroid cancer. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. baseline. ## $p < 0.01$ vs. 1 month after lenvatinib therapy.

significantly lower than that at 1 month ($p < 0.01$). On the other hand, in patients who discontinued lenvatinib therapy prior to 1 year, both Ang-1 and Ang-2 levels 1 month after treatment were significantly lower than those at baseline ($p < 0.01$ and $p < 0.05$, respectively).

None of the 10 patients with anaplastic thyroid cancer continued treatment with lenvatinib for more than 1 year ($p = 0.002$ in Table II). Therefore, subgroup analyses were performed only on the 21 patients with papillary thyroid cancer (PTC) or follicular thyroid cancer (FTC) (Table II, lower berth). Similar to the results from the 36 patients with five different histological types of thyroid cancer, there were no significant differences in Ang-1 and Ang-2 levels at baseline or at 1 month after initiation of lenvatinib therapy. Similarly, there were no significant differences in the rates of change at 1 month relative to baseline between these 2 groups. However, Ang-2 levels at 1 month after treatment initiation were significantly lower than those at baseline ($p < 0.001$).

Discussion

In the present study, we found that Ang-2 levels were significantly reduced following the administration of lenvatinib. Especially in patients that achieved PR to lenvatinib therapy, Ang-2 levels were significantly decreased. A cut-off value for the rate of decrease in Ang-2 from baseline to attain PR to lenvatinib therapy was -49.83% according to the ROC analysis. We hypothesized that monitoring Ang-2 levels at 2 sampling points, before initiation of therapy and at 1 month after initiation, might allow prediction of clinical outcomes following Lenvatinib therapy. However, prediction of efficacy for lenvatinib using Ang-2 levels may only be possible 1 year after initiation of lenvatinib administration. In the present study, we found that Ang-2 levels at 1 year tend to increase compared with those at 1 month (rate of change for patients with PR: -40.2% from -51.8%; for patients with SD: -36.9% from -39.8%; and for

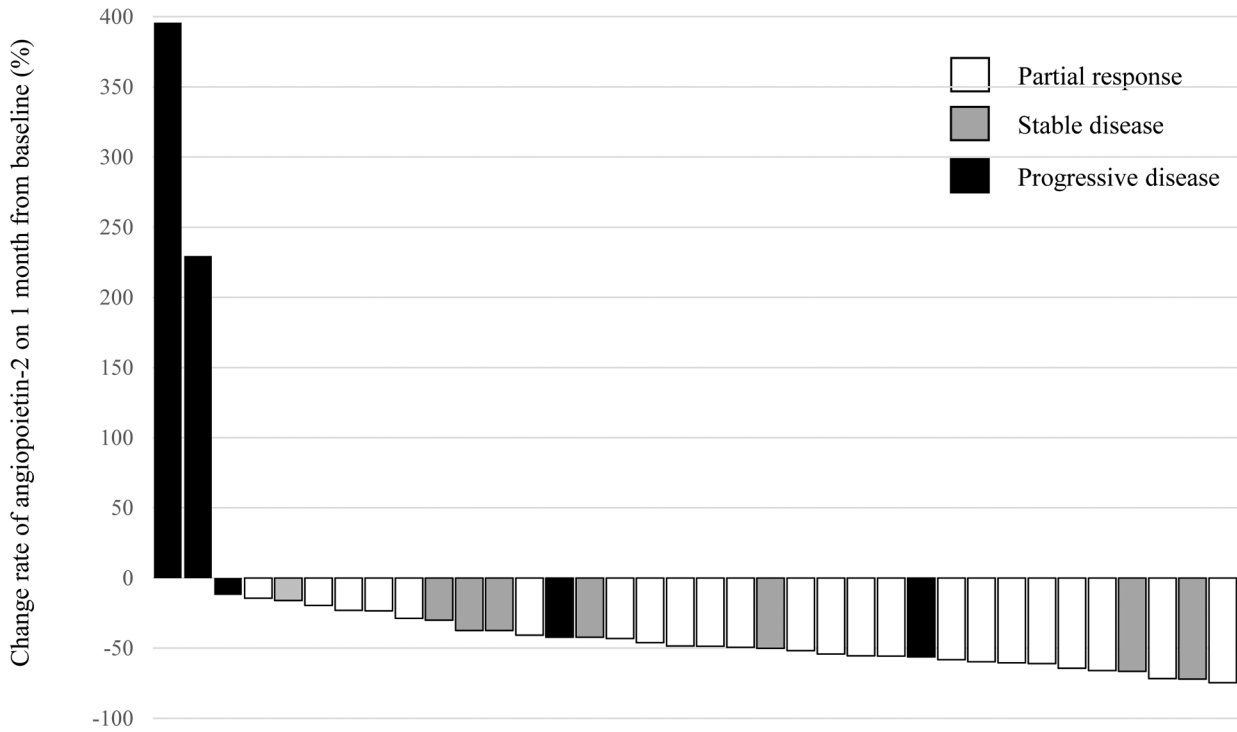


Figure 2. Waterfall plot of the rate of change of angiopoietin-2 1 month after initiation of lenvatinib treatment from baseline in 36 patients.

patients continued therapy for 1 year: -40.2% from -51.0%). Increased Ang-2 levels after lenvatinib therapy may correlate with tumor progression and OS.

Although Ang-2 levels were significantly reduced by the administration of lenvatinib, Ang-1 levels were not significantly changed by lenvatinib. Therefore, changes of the Ang-2/Ang-1 ratio following lenvatinib treatment depended on the change of Ang-2 levels. Our present study indicated that Ang-2 better predicted the efficacy of lenvatinib in patients with thyroid cancer than did either Ang-1 or the Ang-2/Ang-1 ratio. Previously, Ang-2 levels were reported to be associated with tumor angiogenesis in hepatocellular carcinoma (16), lung tumors (17) and colorectal cancers (18), and the relationships between Ang-2 levels at pre-therapy and clinical outcomes after drug therapy have been investigated (10, 19, 20). In a phase 3 study of lenvatinib for thyroid cancers, a significant association between Ang-2 levels at pre-therapy of lenvatinib and clinical outcomes were also observed (9, 10). However, in the present study, there were no significant differences in Ang-2 levels at baseline among patients with PR, SD and PD or among patients who continued lenvatinib therapy longer than 1 year.

In two patients with higher Ang-2 levels of 8,011 and 7,174 pg/ml at baseline there was a decrease to 3,568 and 3,686 pg/ml, respectively, at 1 month and then to 2,593 and

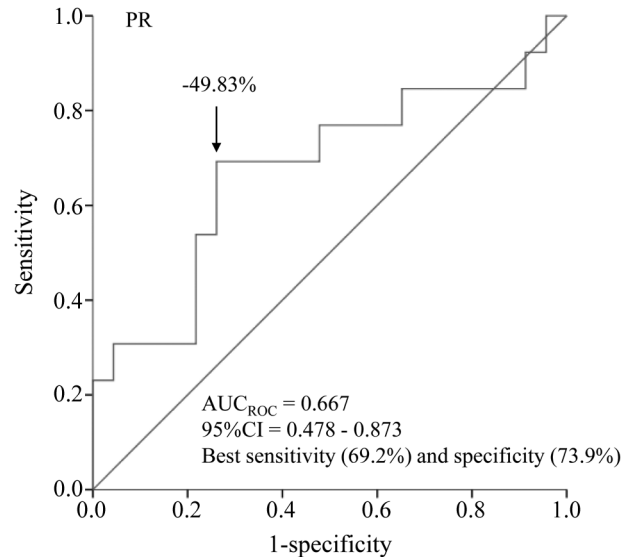


Figure 3. Receiver operating characteristic (ROC) analyses of the performance of the threshold of the rate of change of angiopoietin-2 in the prediction of partial response.

3,011 pg/ml, respectively, at 1 year after the start of lenvatinib therapy. Thus, the efficacy of PR to lenvatinib in patients with higher Ang-2 levels at baseline was confirmed.

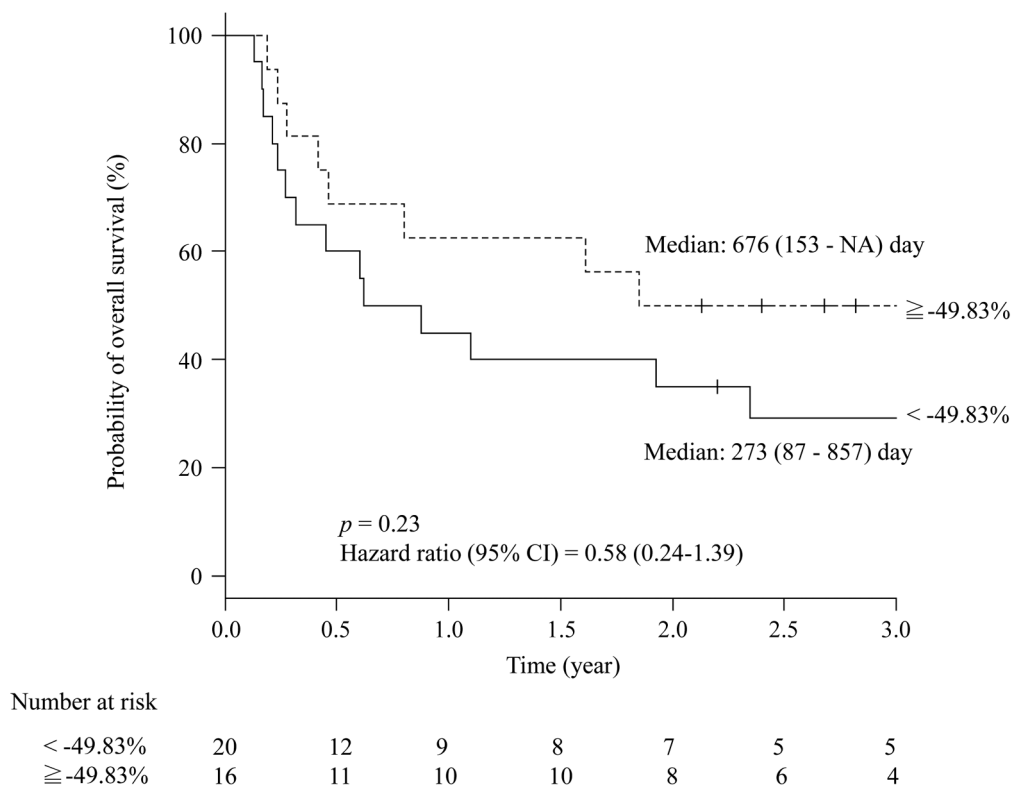


Figure 4. Kaplan–Meier curve of overall survival (OS) according to thresholds of the rate of change of angiotensin-converting enzyme 2 (ACE2) of at least -49.83% (dotted line) and less than -49.83% (black line).

However, in patients with Ang-2 levels of 2,280 and 3,493 pg/ml at baseline there was an increase to 11,305 and 11,511 pg/ml, respectively, at 1 month after initiation of lenvatinib therapy, and these patients were non-responders to lenvatinib and developed PD. Therefore, the rate of change of Ang-2 at 1 month after treatment initiation from baseline rather than a single data point consisting of the Ang-2 level at baseline may be important as a biomarker of the inhibitory effect of Lenvatinib on angiogenesis. Notably, thyroglobulin levels and the neutrophil to lymphocyte ratio (NLR) are also considered to be biomarkers of the clinical effects of lenvatinib (21, 22), and, similar to our present results, thyroglobulin levels at 3 months after lenvatinib therapy and NLR in patients that achieved the best tumor response to lenvatinib therapy have been reported to be significantly lower than those pre-therapy (21, 22).

In the present study, we demonstrated a lack of significant correlation between the plasma concentrations of lenvatinib and Ang-2. High plasma levels of lenvatinib therefore seem to be unnecessary to attain clinical responses. The median C_0 of lenvatinib at 1 year in patients with PR (49.7 ng/ml) was significantly lower than those at 1 month after the initiation of treatment (71.2 ng/ml). This decrease in C_0 over time was caused by the dose reduction of lenvatinib due to

the onset of side effects. In addition, the median C_0 of lenvatinib at 1 year in patients who continued treatment more than 1 year (59.7 ng/ml) was significantly lower than those 1 month after treatment (82.0 ng/ml). The target C_0 of lenvatinib, is optimal point of balance between benefit and toxicity; for patients with thyroid cancer the target C_0 is reported to be 51.5 ng/ml (11). The C_0 of lenvatinib of 51.5 ng/ml in these previous studies is similar to the median C_0 at 1 year after treatment in the present study.

As shown in Figure 1, the rate of change of Ang-2 at 1 month after treatment initiation from baseline was decreased to about 44.3% with a C_0 of lenvatinib of 51.5 ng/ml ($y = -0.0352x - 42.533$). This rate of change of Ang-2 from baseline in the context of a C_0 of lenvatinib of approximately 51.5 ng/ml was similar to those in higher contexts of C_0 of lenvatinib of more than 100 ng/ml. Therefore, after beginning treatment with an initial dose of lenvatinib of 24 mg, subsequent required doses may be calculated according to the target C_0 of 51.5 ng/ml early to avoid adverse events of lenvatinib.

Our current findings may be interpreted within the context of a limitation regarding types of thyroid cancer. Different types of thyroid cancer are described according to histological features. These types include well-differentiated

Table II. Association between plasma concentration of angiopoietin-1, -2 and lenvatinib and presence of continuation of lenvatinib therapy during 1 year.

Lenvatinib therapy	Continuous therapy for 1 year		Withdrawal at less than 1 year		p-Value
	Median	18 (Q1-Q3)	Median	18 (Q1-Q3)	
Number					
Age	67.0	(57.8-72.0)	68.0	(59.0-74.0)	0.584
Female:Male		10:8		13:5	0.489
PTC/FTC/MTC/PDTC/ATC		9/5/0/4/0		4/3/1/0/10	0.002
Angiopoietin-1					
Before lenvatinib therapy (baseline) (pg/ml)	6,459	(4,311-7,209)	6,833	(5,250-8,750)	0.118
1 month after lenvatinib treatment (pg/ml)	5,750	(4,146-7,250)	5,417	(4,667-6,083)**	0.406
1 year after lenvatinib treatment (pg/ml)	5,625	(4,490-7,458)			
Change on 1 month from baseline (%)	-9.2	(-19.8-10.1)	-25.1	(-34.0-1.6)	0.068
Change on 1 year from baseline (%)	3.3	(-18.0-20.4)			
Angiopoietin-2					
Before lenvatinib therapy (baseline) (pg/ml)	1,590	(1,375-2,237)	1,773	(1,205-2,986)	1.000
1 month after lenvatinib treatment (pg/ml)	968	(687-1,245)***	936	(830-1,649)*	0.673
1 year after lenvatinib treatment (pg/ml)	1,015	(887-1,394)***			
Change on 1 month from baseline (%)	-51.0	(-60.0- -35.2)	-46.1	(-58.2- -16.1)	0.501
Change on 1 year from baseline (%)	-40.2	(-53.8- -29.1)			
Angiopoietin-2/angiopoietin-1 ratio					
Before lenvatinib therapy (baseline)	0.30	(0.19-0.52)	0.28	(0.20-0.42)	0.584
1 month after lenvatinib treatment	0.13	(0.12-0.35)***	0.22	(0.13-0.33)	0.443
1 year after lenvatinib treatment	0.19	(0.14-0.25)***			
Lenvatinib					
C ₀ on 1 month after lenvatinib treatment (ng/ml)	82.0	(64.7-181)	108	(58.3-152)	0.606
C ₀ on 1 year after lenvatinib treatment (ng/ml)	59.7	(37.0-113)##			
PTC/FTC		9/5		4/3	1.000
Angiopoietin 1					
Before lenvatinib therapy (baseline) (pg/ml)	6,459	(4,224-8,083)	6,833	(5,250-8,750)	0.322
1 month after lenvatinib treatment (pg/ml)	6,084	(3,771-7,250)	5,326	(4,917-6,648)	0.743
Change on 1 month from baseline (%)	-10.8	(-19.8-4.9)	-28.0	(-42.9-4.4)	0.172
Angiopoietin 2					
Before lenvatinib therapy (baseline) (pg/ml)	1,790	(1,448-2,237)	1,752	(1,399-3,493)	0.799
1 month after lenvatinib treatment (pg/ml)	999	(754-1,387)***	1,212	(886-11,305)	0.197
Change on 1 month from baseline (%)	-45.9	(-54.4- -27.5)	-30.0	(-49.4-230)	0.197

Q: Quartile; PTC: papillary thyroid cancer; FTC: follicular thyroid cancer; MTC: medullary thyroid cancer; PDTC: poorly differentiated thyroid cancer; ATC: anaplastic thyroid cancer. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. baseline. ## $p < 0.01$ vs. 1 month after lenvatinib therapy.

papillary thyroid cancer, which makes up 75 to 80% of thyroid cancer cases, follicular thyroid cancer (8 to 10%), poorly differentiated thyroid cancer (5 to 7%), medullary thyroid cancer (5 to 7%) and anaplastic thyroid cancer (2 to 3%) (23). Lenvatinib is approved for anaplastic thyroid cancer in Japan and lenvatinib is used for all histological types of thyroid cancer. Therefore, we analyzed data without separating different histological types; however, additional studies in different histological types of thyroid cancer may be necessary.

Conclusion

The rate of change of Ang-2 levels at 1 month after treatment from baseline did not correlate with the lenvatinib C₀ at the same time; however, Ang-2 levels were significantly reduced by the administration of lenvatinib. In particular, Ang-2 levels in patients with PR to lenvatinib therapy or patients who continued treatment with lenvatinib for 1 year were significantly decreased. The rate of change of Ang-2 at 1 month after treatment from baseline may be

important as a biomarker of the inhibitory effect of lenvatinib on angiogenesis.

Conflicts of Interest

All Authors have no conflicts of interest and have no relevant relationships to disclose in relation to this study.

Authors' Contributions

MK, MN, YA, 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 collection of patients and were involved in acquisition of data. MK, YA and MM analyzed plasma concentrations. MK and MM were responsible for the statistical analyses. MK, MN, and MM drafted the manuscript. AS, KS, TO, YA, and KI helped to draft the manuscript. All Authors read and approved the final manuscript.

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