

Rapid disease progression after discontinuation of lenvatinib in thyroid cancer

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Abstract

Some thyroid cancer patients experience a rapid disease progression after the discontinuation of tyrosine kinase inhibitors (TKIs), which is called flare phenomenon. The incidence of the flare phenomenon of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) ranged from 4% to 11.1% and the median time to occurrence of the flare phenomenon ranged from 7 to 12 days in previous reports. In this study, we investigate the timing and incidence of the flare phenomenon in thyroid cancer patients treated with lenvatinib.

The records of patients treated with lenvatinib were retrospectively reviewed. The primary outcomes were the incidence rate and timing of the flare phenomenon after the discontinuation of lenvatinib. The flare phenomenon was defined as death, hospitalization attributable to tumor progression, or unexpected event (e.g., pleural drainage) within 1 month of lenvatinib cessation. We excluded patients with progression of underlying diseases other than thyroid cancer or infection, those in whom the disease progressed, or those who died without achieving a clinical response (stable disease, partial response, or complete response).

In total, 8 (14.3%) of the 56 patients experienced the flare phenomenon. The median time from lenvatinib cessation to the flare phenomenon was 9 (range, 4–30) days. Three patients in the flare group died within 1 month of lenvatinib cessation without an imaging evaluation. The remaining 5 patients had dyspnea and pleural effusion, and pleural drainage was performed in 3 of the 5 patients. Lenvatinib was resumed in 4 of the 8 patients in the flare group. Median overall survival (OS) was 15.1 months in the flare group and 41.9 months in the non-flare group. The OS tended to be poor in the flare group than in the non-flare group; however, this difference was not statistically significant ($P = .051$).

In lenvatinib treatment for thyroid cancer, the incidence and timing of the flare phenomenon were similar to those observed with other TKIs. OS tended to be poor in the flare group than in the non-flare group. Further studies are needed to determine the mechanism of the flare phenomenon and establish measures and treatment policies.

Abbreviations: DTC = differentiated thyroid carcinoma, EGFR = epidermal growth factor receptor, OS = overall survival, PDGFRa = platelet-derived growth factor receptor a, PS = performance status, RAI = radioactive iodine, SELECT = Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid, TKI = tyrosine kinase inhibitor.

Keywords: differentiated thyroid carcinoma, flare phenomenon, lenvatinib, tyrosine kinase inhibitors

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1. Introduction

Lenvatinib inhibits the kinase activities of vascular endothelial growth factor receptors 1, 2, and 3; fibroblast growth factor receptors 1 to 4; platelet-derived growth factor receptor a (PDGFRa), and RET and KIT signaling networks. The Study of Lenvatinib (E7080) in Differentiated Cancer of the Thyroid (SELECT) trial was a multinational phase 3 trial, in which lenvatinib showed a significant antitumor activity. The median progression-free survival was 18.3 months in lenvatinib and 3.6 months in placebo groups. The hazard ratio for progression or death was 0.21 (99% confidence interval, 0.14–0.31; $P < .001$). The lenvatinib response, disease control, and clinical benefit rates were 64.7%, 87.7%, and 80.1%, respectively.^[1] Lenvatinib is also known to exert significant antitumor activity against all histological types of thyroid carcinoma and is presently used in clinical practice.^[2] Some thyroid cancer patients experience a flare phenomenon or rapid disease progression after the discontinuation of treatment with tyrosine kinase inhibitors (TKIs). Uchida et al reported a case of pleural effusion that occurred after the discontinuation of lenvatinib in a patient with poorly differentiated thyroid cancer.^[3] The available evidence

shows that some, but not all, patients treated with TKIs experience the flare phenomenon after the discontinuation of treatment.^[4] Although lenvatinib treatment has been associated with frequent treatment-related adverse events, the occurrence of flare phenomenon has not been reported.^[5] We conducted a retrospective study to investigate the timing and incidence of the flare phenomenon in thyroid cancer patients treated with lenvatinib, which is currently unclear.

2. Materials and methods

2.1. Patients

The institutional review board of Ito Hospital, Tokyo, Japan approved the protocol of this retrospective cross-sectional study. The medical records of thyroid cancer patients treated with lenvatinib from May 2015 to June 2019 were retrospectively reviewed. Patients with histologically or cytologically confirmed thyroid cancer, prior thyroidectomy, ≥ 18 years of age, and treated with radioactive iodine (RAI) for differentiated thyroid carcinomas (DTCs) prior to lenvatinib were included in the study. The patients included in this study were resistant to RAI. The definitions of RAI refractory were as follows:

- (1) The absence of initial RAI uptake in metastases.
- (2) Absence of RAI uptake in metastases after treatment with RAI.
- (3) Presence of RAI uptake in some metastases, but absence in others.
- (4) Progression despite RAI uptake in all metastases.^[6]

Patients with anaplastic thyroid carcinoma were excluded. Demographic and clinicopathological information, such as patient sex, age, Eastern Cooperative Oncology Group performance status (PS), histological type of thyroid cancer, distant metastasis sites, clinical response to lenvatinib, and overall survival (OS) were analyzed. The clinical responses to lenvatinib were evaluated by computed tomography using the Response Evaluation Criteria in Solid Tumors, version 1.1.^[7] The initial dose of lenvatinib was 24 mg/day, and the dose was adjusted in response to the occurrence of adverse events.

2.2. Objectives

The primary outcomes were the incidence rate and timing of the flare phenomenon after the discontinuation of lenvatinib.

2.3. Definitions

Based on previous reports, the flare phenomenon was defined as death, hospitalization attributable to tumor progression, or unexpected event (e.g., pleural drainage) within 1 month of lenvatinib cessation.^[8–10] We excluded patients with progression of underlying diseases other than thyroid cancer or infection, those in whom the disease progressed, or those who died without achieving a clinical response (stable disease, partial response, or complete response). OS was calculated as the time from the start of lenvatinib to the date of death from any cause.

2.4. Statistical analysis

The statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for

Statistical Computing, Vienna, Austria). More precisely, EZR is a modified version of R commander designed to add statistical functions used frequently in biostatistics.^[11] Between-group differences in patient characteristics were tested for significance. Categorical variables were compared with Fisher's exact test; continuous variables were compared with Student's *t* test. An OS curve was constructed with the Kaplan–Meier method. *P* value of $<.05$ was considered statistically significant.

3. Results

3.1. Study population

The patient characteristics are shown in Table 1. In total, 8 (14.3%) of the 56 patients experienced the flare phenomenon. There were no significant differences in baseline characteristics between the 2 groups. The characteristics of the flare group are shown in Table 2. The median duration of lenvatinib treatment was 13.3 (range, 1.6–15.2) months before flare phenomenon. Four patients in the flare group showed partial response, and 4 showed stable disease. The median lenvatinib dose before flare was 13 (range, 8–24) mg/day. The median time from lenvatinib cessation to the flare phenomenon was 9 (range, 4–30) days. The causes for interruption were as follows: 4 patients developed grade 3 proteinuria, 2 became too ill to continue treatment on account of disease progression, 1 developed a fistula, and 1 developed hypoalbuminemia. Three patients in the flare group died within 1 month of lenvatinib cessation without an imaging evaluation. The remaining 5 patients had dyspnea and pleural effusion, and pleural drainage was performed in 3 of the 5 patients. Lenvatinib was resumed in 4 of the 8 patients in the flare group. Median OS was 15.1 months in the flare group and 41.9 months in the non-flare group. The OS tended to be poor in the flare group than in the non-flare group; however, this difference was not statistically significant ($P=.051$) (Fig. 1).

Table 1
Patient characteristics.

	All (n = 56)	Non-flare (n = 48)	Flare (n = 8)	<i>P</i> value
Sex				1
Male	21 (38%)	18 (38%)	3 (38%)	
Female	35 (62%)	30 (62%)	5 (62%)	
Age (years), median (range)	68.5 (33–86)	67 (33–86)	69.5 (49–78)	.568
ECOG performance status				.705
0	28 (50%)	23 (48%)	5 (62%)	
≥ 1	28 (50%)	25 (52%)	3 (38%)	
Histologic type				.059
PTC	32 (57%)	26 (54%)	6 (75%)	
FTC	18 (32%)	18 (38%)	0	
PDTC	5 (9%)	3 (6%)	2 (25%)	
MTC	1 (2%)	1 (2%)	0	
Previous tyrosine kinase inhibitor				1
Sorafenib	2 (4%)	2 (4%)	0	
Distant metastasis				.413
Lung	48 (86%)	40 (83%)	8 (100%)	
Bone	29 (52%)	28 (58%)	1 (13%)	
Lymph node	16 (29%)	15 (31%)	1 (13%)	
Liver	8 (14%)	7 (15%)	1 (13%)	
Brain	3 (5%)	3 (6%)	0	

ECOG=Eastern Cooperative Oncology Group, FTC=follicular thyroid carcinoma, MTC=medullary thyroid carcinoma, PDTC=poorly differentiated thyroid carcinoma, PTC=papillary thyroid carcinoma.

Table 2
The characteristics of the flare group.

No.	Lenvatinib duration before flare (months)	Best clinical response	Lenvatinib dose before flare (mg/day)	Flare phenomenon	Treatment after flare
1	2.2	SD	20	Pleural effusion	Pleural drainage, pleurodesis, and lenvatinib resumption
2	14.9	SD	8	Pleural effusion	Sorafenib
3	13.0	PR	14	Death	
4	13.8	PR	12	Death	
5	13.6	PR	8	Pleural effusion	Pleural drainage and lenvatinib resumption
6	15.2	SD	12	Pleural effusion	Pleural drainage, pleurodesis, and lenvatinib resumption
7	1.6	PR	20	Pleural effusion	Lenvatinib resumption
8	4.9	SD	24	Death	

PR=partial response, SD=stable disease.

4. Discussion

In this study, the incidence rate of the flare phenomenon was 14.3% and the median time of occurrence of the flare phenomenon was 9 days after the discontinuation of lenvatinib. Because there were no significant differences in the baseline characteristics between patients with and without the flare phenomenon, prediction of the occurrence flare phenomenon seemed to be difficult using patient characteristics. Notably, not all cases experience the flare phenomenon after the discontinuation of TKIs^[4]; however, the flare phenomenon did not have a significant effect on OS in this study. We think that the short observation period and small number of cases affected this result.

In a previous report, only 1 case experienced the flare phenomenon after the discontinuation of lenvatinib treatment in thyroid cancer patients. Uchida et al reported the rapid occurrence of pleural effusion 7 days after the discontinuation of lenvatinib in a patient with poorly differentiated thyroid cancer, with improvement in symptoms via pleural drainage and the resumption of lenvatinib.^[3] The timing in this study was similar to that in our study. The flare phenomenon was previously reported in a thyroid cancer patient following

sorafenib cessation.^[12] To the best of our knowledge, this study is the first study to report the incidence of flare phenomenon associated with lenvatinib treatment in thyroid cancer patients.

Several reports of TKI flare have been reported in lung cancer patients. Chaft et al reported an incidence of the flare phenomenon of 23% and a median time to occurrence of the flare phenomenon of 8 days after the discontinuation of an epidermal growth factor receptor (EGFR)-TKI in EGFR-mutant lung cancer patients.^[8] In a series of Asian patients, the incidence of the flare phenomenon after the discontinuation of EGFR-TKI ranged from 4% to 11.1% and the median time to occurrence of the flare phenomenon ranged from 7 to 12 days.^[9,10,13] The incidence rates of the flare phenomenon were lower in Asian patients than in American patients, which might have been affected by the difference in the definition of the flare phenomenon in each study, in addition to the influence of race. The definition of the flare phenomenon used in this study is based on these previous studies.^[8-10,13] The TKIs and the types of cancer were different from those in this study (these previous reports are from non-thyroid cancer patients), but the incidence and timing of the flare phenomenon were similar to those

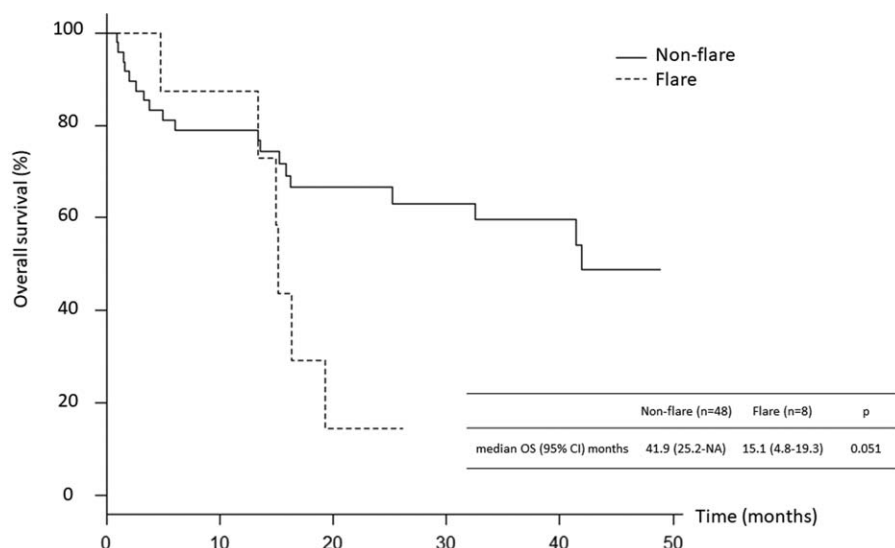


Figure 1. Overall survival of the flare and non-flare groups. Median overall survival was 15.1 months in patients with flare and 41.9 months in those without flare ($P=.051$).

previously reported in Asian patients. A prospective observational study has been conducted to collect the safety and efficacy data of DTC patients receiving lenvatinib to identify the predictors of antitumor activity and survival.^[14] It is expected that the incidence and timing of the flare phenomenon will be investigated from the results of this prospective study.

In our study, the shortest discontinuation period was 4 days in the flare group. Lenvatinib is known to be associated with a high rate of drug interruption and therefore it is necessary to ensure care regarding the occurrence of the flare phenomenon, despite the discontinuation period being short.^[11] The mechanism and risk factors of the flare phenomenon are not yet understood. Anaplastic transformation is known for the rapid progression of disease and is a unique phenomenon in the clinical practice of thyroid cancer.^[15] The histological types of cancer in the patients in this study had been confirmed by prior cytology or thyroidectomy. However, when the distant metastases that were the target lesions in this study rapidly progressed, the biopsies could not be performed to confirm the histological types of the distant metastases. Moreover, the possibility of certain gene mutations induced by lenvatinib or associated with anaplastic transformation cannot be excluded because lenvatinib blocks a variety of signaling pathways. Further, it may be difficult to distinguish the flare phenomenon and anaplastic transformation in imaging studies.

Symptomatic treatment or resumption of TKIs can be treatment options after the occurrence of the flare phenomenon. In a previous case report, chest drainage and the resumption of lenvatinib were performed.^[3] Moreover, switching to another TKI is another treatment option. Reportedly, EGFR-mutant cells that were resistant to gefitinib can become sensitive again following the absence of TKI.^[9] Resumption of TKI treatment may be effective even if the disease has progressed. Kim et al reported that alternating sorafenib and lenvatinib treatment for refractory thyroid cancer is more effective than treatment with either sorafenib or lenvatinib alone in inhibiting cancer progression by inducing cell cycle arrest.^[16] Further studies are needed to determine the better option between the resumption of same TKI and alteration to another TKI, in case of the occurrence of rapid disease progression.

There were some limitations to this study. First, this study was a retrospective study conducted at a single center with a small number of patients. We think that the small numbers of patients affected the outcome that OS was not significantly different between 2 groups. Second, molecular mechanism underlying the flare phenomenon after TKI discontinuation remains unclear. Third, the varied backgrounds of patients may have affected the results. Finally, the accuracy of the definition of flare phenomenon is uncertain. Further, because we did not perform autopsy imaging, the increase in the target lesions could not be confirmed.

5. Conclusion

In lenvatinib treatment for thyroid cancer, the incidence and timing of the flare phenomenon were similar to those observed with other TKIs. OS tended to be poor in the flare group than in the non-flare group. Further studies are needed to determine the mechanism of the flare phenomenon and establish measures and treatment policies.

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