

Age, Symptomatic Metastatic Disease, and Malignant Pleural Effusion as Predictors of Poor Prognosis in Patients with Differentiated Thyroid Carcinoma Treated with Lenvatinib.

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Background: Lenvatinib is one of the few therapeutic options available for radioiodine-refractory thyroid cancer. However, the factors that determine the therapeutic outcomes remain unknown.

Methods: Patients with thyroid carcinoma treated with lenvatinib who had been dead or who had survived for longer than a half-year were retrospectively compared. We evaluated the clinical parameters when lenvatinib was started, and also studied the tumor volume reduction ratio, the duration until re-growth of the largest metastatic lesion, the thyroglobulin (Tg) reduction rate, and the duration until re-elevation of Tg after lenvatinib between survivors and dead patients.

Results: We identified 16 patients, with an average age of 73.1±7.6 yrs and a male-to-female ratio of 5 to 11, who had advanced differentiated thyroid cancer that was treated with lenvatinib. Nine patients had died after 8.9±6.1 months, whereas 7 survived for 13.0±2.0 months after starting lenvatinib. The patients who died were older than the survivors (76.7±6.5 vs. 68.6±6.6 yrs, $p=0.03$). Malignant pleural effusion ($p=0.017$) and symptomatic metastatic disease (SMD) ($p=0.039$) were associated with death in a Kaplan-Meier survival analysis. Age ($p=0.012$, HR 1.150, CI 1.030-1.320) and SMD ($p=0.014$, HR 8.069, CI 1.503-61.34) were associated with poor outcome in a multivariate Cox proportional hazard model. The duration until the re-elevation of Tg was longer in survivors than in patients who died (6.43±4.55 vs. 2.17±1.39 months, $p=0.025$).

Conclusions: We identified multiple factors, including SMD, that were related to poor outcomes after lenvatinib treatment. This study suggests that lenvatinib might be started before patients develop SMD.

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Introduction

Differentiated thyroid carcinoma (DTC) is classified histologically as papillary thyroid carcinoma, follicular thyroid carcinoma, or poorly differentiated thyroid carcinoma. DTC accounts for 95% of all thyroid cancer and is known to have a favorable prognosis, with the 10-year survival rate being 90% or more (1, 2). This survival rate is mainly achieved by surgery and radioiodine (RAI) therapy. However, approximately

5% of patients with DTC present with locally advanced disease (3, 4). According to previous studies, up to 50% of deaths from DTC are caused by active local disease (5). Distant metastasis occurs in 4-10% of patients with DTC and is another major cause of cancer-related death (6-9). Two-thirds of locally advanced or distant metastases of DTC have low avidity for iodine and become refractory to RAI therapy (10). The 10-year survival rate from the time of detection of metastasis among patients with RAI-refractory

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DTC is much lower, nearly 10% (10-12). Until recently, there were few treatment options for patients with RAI-refractory and progressive DTC.

Recent advances in the understanding of the oncogenic pathways of thyroid tumors have enabled the development of targeted therapies for progressing RAI-refractory DTC. The most frequent genetic alterations that have been found are RET-PTC translocation and BRAF^{V600E} point mutations in papillary thyroid carcinoma and RAS point mutations in follicular and poorly differentiated thyroid carcinoma. Most of these genetic events involve genes with kinase activity and are associated with the MAP kinases and/or the PI3K/Akt/mTOR signaling cascades. The activation of these pathways has been shown to induce neoplastic transformation and progression (13). DTC is also known to harbor mutations in or over-expression of some cell-surface receptors such as vascular endothelial growth factor receptors (VEGFRs) 1-3, fibroblast growth factor receptors (FGFRs) 1-4, and platelet-derived growth factor receptor alpha (PDGF-R α) (13,14). These signaling networks have been associated with tumor angiogenesis, and therefore, multi-targeted tyrosine kinase inhibitors (m-TKIs) have been developed to regulate these inappropriately activated pathways.

Lenvatinib and sorafenib are m-TKIs which target both tumorigenic and angiogenic molecules and are approved for the treatment of patients with progressive RAI-refractory locally advanced or metastatic DTC in Japan. Sorafenib is a m-TKI that targets VEGFR 1-3, RET, RAF, and PDGF-R β , whereas lenvatinib targets VEGFR 1-3, FGFR 1-4, RET, KIT, and PDGF-R α . Sorafenib treatment has been shown to significantly improve the median progression-free survival (10.8 months vs 5.8 months) with a partial response rate (12.2% vs 0.5%) compared with placebo in the randomized, double-blind, phase III DECISION trial (14). In the phase III SELECT trial, it was demonstrated that lenvatinib improved the median progression-free survival (18.3 months vs 3.6 months) with a partial response rate (64.8% vs 1.5%) compared with placebo, and it was also shown that 4 patients treated with lenvatinib responded completely (15). Although no head-to-head data exist comparing sorafenib with lenvatinib, lenvatinib seems to be more effective for DTC.

The initiation of m-TKIs therapy should be considered carefully because m-TKIs have frequent adverse events such as hypertension, hand-foot skin reaction, diarrhea, and fatigue (14-16). The National Comprehensive Cancer Network guidelines state that m-TKIs therapies should be considered for progressive and/or symptomatic RAI-refractory DTC (17). The current American Thyroid Association guideline also recommends m-TKIs therapy for patients with imminently

threatening disease progression that is expected to require intervention and/or to produce morbidity or mortality in <6 months, or symptomatic disease (18). In contrast, a recent study from Japan implies that the clinical benefits of m-TKIs therapy might be limited when the therapy starts after tumor-mediated symptoms appear (19).

In this retrospective study, we investigated the clinical factors related to the outcomes of patients treated with lenvatinib and attempted to identify the optimal timing for the start of lenvatinib.

Patients and Methods

Patients

Patients with thyroid carcinoma treated with lenvatinib who had been dead or who had survived for longer than a half-year as of October 2017 in our institute were retrospectively studied. When lenvatinib was started, several clinical parameters were recorded in the medical charts. The parameters studied were age, sex, the duration from the initial thyroid operation, symptomatic metastatic disease, the presence of neck metastasis, lung metastasis (inclusion criteria being largest lesion with a diameter larger than 1 cm), malignant pleural effusion, liver metastasis, bone metastasis, and brain metastasis, and prior treatment including RAI therapy, external-beam radiation, and m-TKIs other than lenvatinib.

We also assessed the tumor volume reduction ratio of the largest metastatic lesion and the duration until re-growth of the largest metastatic lesion after the initiation of lenvatinib in each patient. The tumor size was expressed by the product of the long axis and the maximum diameter perpendicular to the long axis of the largest metastatic lesion in the CT images. The tumor volume reduction ratio is expressed as the percentage reduction of the tumor size when the target lesion is reduced maximally after lenvatinib treatment. Tumor re-growth is determined by the CT images in which the largest metastatic tumor which once showed a reduction in tumor size after lenvatinib treatment shows re-enlargement during lenvatinib treatment. The thyroglobulin (Tg) reduction rate and the duration until the re-elevation of Tg were studied only in patients without Tg antibody (TgAb). The Tg reduction rate was calculated based on the nadir Tg after lenvatinib treatment divided by the Tg before the treatment.

Statistical analysis

The clinical parameters at the time the lenvatinib was started were compared between those who survived and

those who died. Data are expressed as the mean \pm standard deviation. Student's t-tests were used to compare continuous variables. Comparisons of independent variables were calculated by Fisher's exact test. Survival after lenvatinib treatment was assessed by the Kaplan-Meier test. Univariate and multivariate Cox proportional hazard models were used to study the influence of clinical parameters on the survival outcome. Independent t-tests were used to compare the tumor volume reduction ratio and the duration until re-growth of the largest metastatic lesion as well as the Tg reduction rate and the duration until re-elevation of Tg after lenvatinib treatment between survivors and patients who died. Values of $P < 0.05$ were considered statistically significant.

Results

We identified 20 patients with advanced thyroid cancer who were treated with lenvatinib. These patients were treated with lenvatinib because of symptomatic metastatic disease and/or progressive metastatic lesions which would be fatal without effective treatments in the near future. The

clinical symptoms that developed were mainly associated with locally progressive disease in the neck and respiratory symptoms associated with lung metastasis and/or malignant pleural effusion. The patients were given a full explanation of the potential benefits and side effects of lenvatinib treatment and their prognosis including the presumed clinical course if left untreated. Four patients were excluded from the analysis because they had anaplastic thyroid carcinoma ($n=2$) or medullary thyroid carcinoma ($n=2$).

The 16 patients included had an average age of 73.1 ± 7.6 yrs and a male-to-female ratio of 5 to 11. Nine patients had died due to progression of thyroid carcinoma after 8.9 ± 6.1 months, whereas 7 survived for 13.0 ± 2.0 months after starting lenvatinib. The patients who died were older than the survivors (76.7 ± 6.5 vs. 68.6 ± 6.6 , $p=0.029$) when they started lenvatinib. Other clinical factors were similar between the two groups (Table 1).

The starting dose of lenvatinib was a full dose of 24 mg in 7 patients, 14 mg in 2 patients, and 10 mg in 7 patients. The reason for the reduction was due to hemoptysis and inactive brain metastasis in two patients who started with 14 mg. All outpatients who started lenvatinib started with

Table 1. Clinical parameters of patients with thyroid cancer treated with lenvatinib.

	Survived (N=7)	Dead(N=9)	P
Age	68.6 \pm 6.6	76.7 \pm 6.5	0.029
Sex(M/F)	2/5	3/6	N.S.
Tissue type (pap/fol/po)	5/1/1	7/1/1	N.S.
Duration after the first operation (year)	10.3 \pm 7.4	10.2 \pm 5.0	N.S.
Metastasis in			
Neck	4	6	N.S.
Lung (>1cm)	2	6	N.S.
Pleura	0	4	N.S.
Bone	4	3	N.S.
Brain	2	1	N.S.
Liver	0	1	N.S.
Symptomatic metastasis	2	5	N.S.
Treatment prior to lenvatinib			
Radioiodine therapy	6	6	N.S.
External Beam Radiation	4	3	N.S.
Multiple Kinase Inhibitor	0	3	N.S.

Patients included were those who had been dead after lenvatinib treatment and those who survived for longer than a half-year after lenvatinib treatment.

pap/fol/po indicate the histology type of thyroid cancer, namely, papillary, follicular, and poorly differentiated thyroid carcinoma, respectively. N.S. indicates not significant.

10 mg of the reagent. This was because after our experience with using the full dose of lenvatinib, we learned that a decreased dose of the reagent would be realistic since the full dose commonly caused serious adverse effects of appetite loss which interrupted the treatment for long periods. The starting dose was 19.78 ± 6.44 mg and 12.57 ± 5.25 mg in the patients who died and those who survived, respectively ($p=0.03$). The doses of lenvatinib were 206.9 ± 98.54 and 128.7 ± 100.46 mg a month in the patients who died and those who survived, respectively. The difference was not significant. There were interruptions of the lenvatinib treatment for various reasons in 5 out of the 9 patients who died and 4 out of the 7 who survived. We also noticed that some patients terminated the lenvatinib treatment. One patient who died terminated the treatment because the cancer did not respond to lenvatinib. Two survivors also terminated the treatment because of adverse effects in one (appetite loss and mucocutaneous symptoms) and non-responding cancer in the other.

Adverse events associated with lenvatinib treatment were frequently seen. The common events were hypertension, seen in 14 patients, appetite loss in 7 patients, mucocutaneous symptoms including hand-foot syndrome in 5 patients, and thrombocytopenia in 5 patients.

We studied the influence of the clinical parameter values before starting lenvatinib on the outcome of the treatment. We found that malignant pleural effusion ($p=0.017$) and symptomatic metastatic disease ($p=0.039$) were associated with the outcome of death in Kaplan-Meier survival analysis (Figure 1). In the univariate Cox proportional hazard model, malignant pleural effusion ($p=0.041$, HR 4.56, CI 1.069-19.489) was associated with poor outcomes, but symptomatic

metastatic disease and age were not. In the multivariate Cox proportional hazard model, age ($p=0.012$, HR 1.150, CI 1.030-1.320) and symptomatic metastatic disease ($p=0.014$, HR 8.069, CI 1.503-61.34) were associated with poor outcomes.

We then compared the response of thyroid cancer to lenvatinib between patients who died and those who survived. The tumor volume reduction ratio was available in 8 patients who died and 7 survivors; there were deficits in the data available after the lenvatinib treatment in two patients who died (D4 and D7) because they were transferred to other hospitals, and there were no images available after the lenvatinib treatment in D4 and no images to determine the tumor re-growth in D7. The tumor volume reduction ratios were $16.91 \pm 53.10\%$ and $10.31 \pm 76.72\%$ in the patients who died and those who survived, respectively ($p=0.73$, Figure 2(a)). In 2 of the patients who died (D1, D9) and 2 of the survivors (S3, S5), lenvatinib was not able to reduce the largest metastatic lesion. The duration until re-growth of the largest metastatic lesion was 4.21 ± 4.54 months and 5.07 ± 5.47 months in the patients who died and those who survived, respectively ($p=0.49$, Figure 2(b)).

We then looked at the changes in Tg before and after lenvatinib treatment. There was no significant difference in the Tg reduction rate between the two groups (patients who died, $59.30 \pm 27.22\%$; surviving patients, $56.7 \pm 24.94\%$; $p=0.86$, Figure 3(a)). The duration until the re-elevation of Tg after lenvatinib treatment was longer in the survivors (6.43 ± 4.55 months) than in the patients who died (2.17 ± 1.39 months). The difference was statistically significant ($p=0.025$, Figure 3(b)).

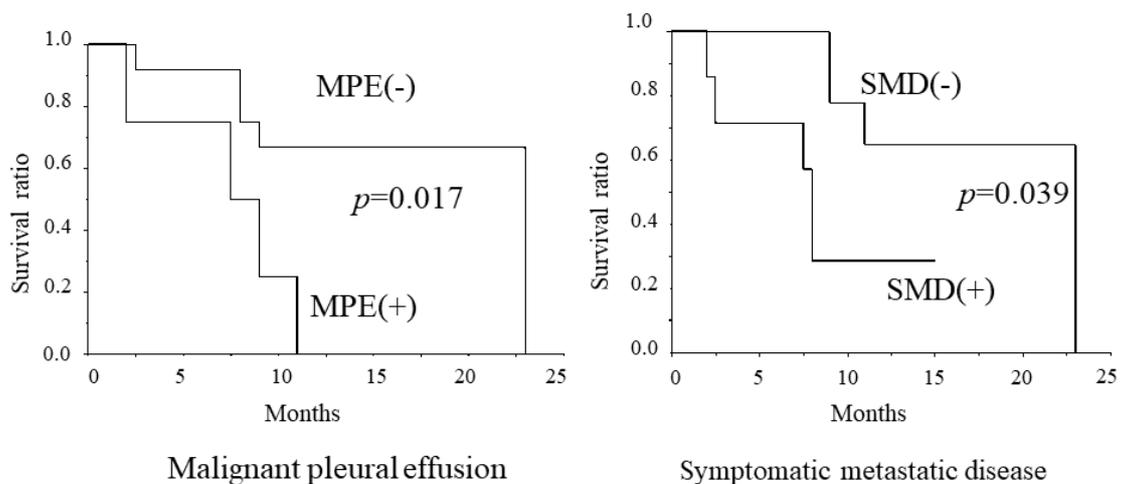


Figure 1. Disease-specific survival of patients with (a) malignant pleural effusion (MPE), and (b) symptomatic metastatic disease (SMD), in Kaplan-Meier survival analysis.

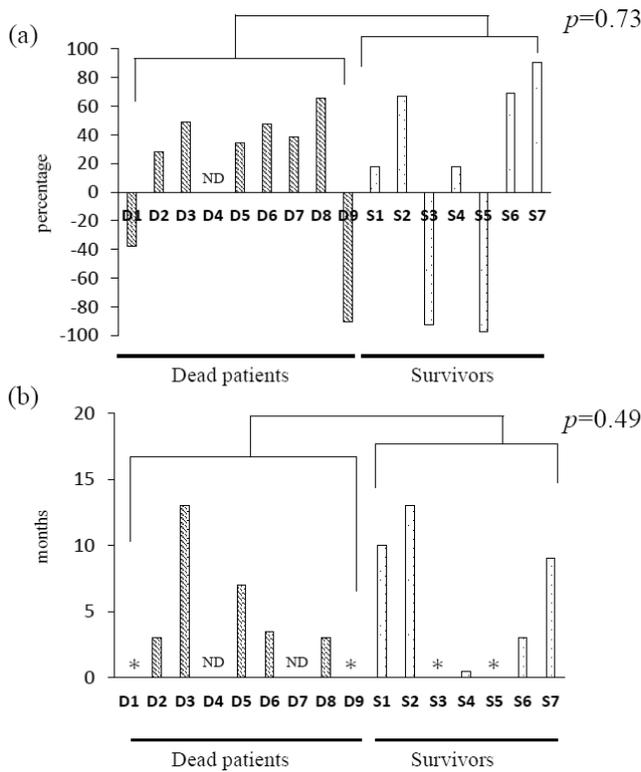


Figure 2. (a) The tumor volume reduction ratio of the largest metastatic lesion after the initiation of lenvatinib. (b) The duration until re-growth of the largest metastatic lesion after the initiation of lenvatinib. * Indicates that the largest metastatic tumor in the indicated patients showed continuous enlargement after lenvatinib treatment. ND: no data.

Discussion

In the current guidelines for thyroid cancer published by the American Thyroid Association and the National Comprehensive Cancer Network, m-TKIs including lenvatinib should be considered in patients such as those with symptomatic and progressive disease (17) and those with a short prognosis (<6 months) if not treated (18). Most of the patients with thyroid cancer would not be able to continue the full dose of lenvatinib (15, 20) and would need several visits to the hospital to adjust the dose of lenvatinib to have anti-tumor effects without serious adverse effects. Thus, for patients with a short expected survival period—6 months for example—it might be too late to start m-TKIs including lenvatinib.

We found that older age was associated with a poor prognosis in thyroid cancer patients treated with lenvatinib. The prognosis of younger patients is known to be favorable because of RAI avidity (10, 21). Older age has been shown to be related with shorter disease-specific survival (22), especially in patients with pulmonary metastases (23, 24).

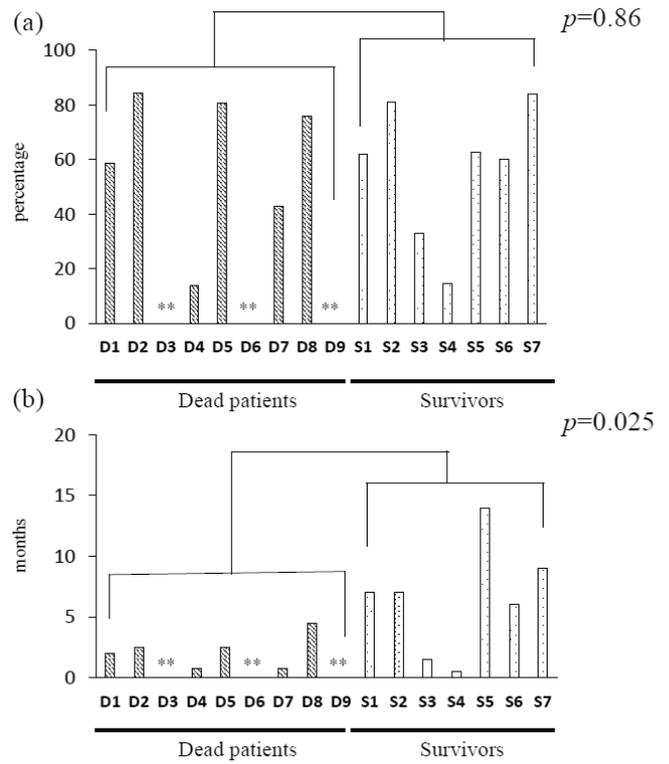


Figure 3. (a) Tg reduction rate. (b) Duration until the re-elevation of Tg. ** Indicate that Patients D3, D6 and D9 were excluded from the analysis because they were positive for TgAb.

The prognosis of such patients would even be poor if lung metastasis develops after the initial RAI therapy (24). In the SELECT trial, however, there were no significant differences in overall survival between age >65 and age ≤65 among patients treated with lenvatinib (25). This was inconsistent with our findings, possibly because our cohort included patients who were much older than those in the SELECT trial. In general, older patients showed a reduced capacity for compensation as well as multiple comorbidities and lower performance status, and these would have influenced their survival.

We found that malignant pleural effusion was related to poor prognosis in patients receiving lenvatinib treatment. Previous reports of malignant pleural effusion in patients with thyroid cancer are limited, but it has been suggested that such patients are at the end stage of thyroid cancer with multiple organ metastases other than in the lung, and thus have a short prognosis (the median survival is around 1 year) (26, 27). Some of our patients showed a reduction of pleural effusion after lenvatinib treatment; however, patients with malignant pleural effusion may experience fewer benefits

from lenvatinib treatment considering their short survival period. It might be more beneficial to start lenvatinib treatment before patients develop malignant pleural effusion.

We also showed that symptomatic metastatic disease was associated with poor outcomes after lenvatinib treatment. Clinical symptoms appear only in patients with fully advanced cancer. It has been shown that death due to thyroid cancer could be associated with massive distant metastasis or local tumor invasion into the trachea and esophagus (28). This is consistent with our findings. Lenvatinib has been shown to decrease the tumor size significantly within a short period of time (15), and we observed considerable symptomatic relief in some of our patients who were treated with lenvatinib. Thus, symptomatic metastatic disease justifies lenvatinib use in patients with advanced DTC. However, this would not justify starting lenvatinib only in patients who had developed symptomatic metastatic disease.

It has been shown that lenvatinib induced an early tumor volume reduction, i.e., objective tumor volume reduction seen within 8 weeks of treatment, in patients with progressive RAI-refractory thyroid cancer (29). Mona et al. very recently reported that m-TKIs prolonged the doubling time of the lung tumor volume, and this was associated with improved disease-specific survival in patients with progressive metastatic RAI-refractory DTC (30). We were not able to show differences in the tumor reduction ratio or the duration until re-growth of the largest metastatic tumor between survivors and patients who died, probably due to the limited number of patients included in this study.

Tg has been established as a tumor marker of DTC. Tg levels are known to increase prior to disease progression (31). The Tg doubling time has been shown to be useful for evaluating the activity of residual thyroid cancer (32). The Tg response after lenvatinib treatment has been shown to occur slightly earlier than the morphologic response (29, 31, 33). Werner et al. showed that the initiation of lenvatinib in patients with progressive RAI-refractory thyroid cancer is associated with a significant reduction in serum Tg levels; thus, Tg could function as a marker of treatment response (33). In our study, Tg reduction rates were not different between survivors and patients who died, but the duration until the re-elevation of Tg after lenvatinib treatment in survivors was significantly longer than in patients who died. This suggests that lenvatinib was effective for a longer period of time in survivors.

There are several limitations to our study, including the retrospective nature of the study design and the fact that the number of patients included was small. The timing with which lenvatinib was started may not have been uniform,

since this was judged by several different clinicians.

In summary, we found three factors that were related to poor outcomes after lenvatinib treatment in patients with advanced DTC. These were older age, pleural effusion, and symptomatic metastatic disease. Considering that most patients require dose adjustment due to the adverse effects of lenvatinib, we suggest that it might be more beneficial to start lenvatinib treatment before patients develop symptomatic metastatic diseases and pleural effusion.

Conflict of Interest

None of the authors have any potential conflicts of interest associated with this research.

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