

Outcome of initial lenvatinib treatment in patients with unresectable anaplastic thyroid cancer

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Abstract. Anaplastic thyroid cancer (ATC) is a very rare disease with a poor prognosis and with no established effective drug therapy. The present study aimed to report the outcomes of lenvatinib single-agent therapy as an initial drug treatment in ATC, and to investigate its safety and efficacy. This retrospective cohort study included 56 patients with unresectable primary ATC, of whom 36 were treated with lenvatinib and 12 with weekly paclitaxel, and 8 patients who refused any drug treatment who received palliative care. The average survival in the lenvatinib group was 5.8 months, which was significantly longer than 2.0 months in the paclitaxel group ($P=0.005$). The efficacy of lenvatinib in the 36 patients with ATC, whose primary tumors were unresectable, was evaluated. The response rate was 33% and the median overall survival time was 5.0 months. A safety review indicated that lenvatinib should be used under the careful observation of local findings. Two patients, who showed a reduction with lenvatinib, underwent conversion surgery, which prolonged the prognosis in terms of avoiding events, such as asphyxia, fistula and hemorrhage due to tumor growth; however, the surgical

margins were positive, indicating that complete remission was impossible even if surgical resection was performed. Therefore, starting with lenvatinib treatment and identifying a therapeutic drug based on genomic analysis is an acceptable treatment strategy for ATC while halting the disease progression.

Introduction

Anaplastic thyroid cancer (ATC) is a very rare disease with a remarkably poor prognosis. The Surveillance, Epidemiology, and End Results database reported a frequency of 0.92 per million patients. The median survival was 3.16 months (1). As an orphan disease, and due to the exceptionally high grade of malignancy, effective drug therapy has not been established for ATC (2). The American Thyroid Association guidelines recommend that genomic analysis should be performed first after diagnosis and a therapeutic drug should be the first choice of treatment if available. In addition, antiangiogenic drugs have the risk of bleeding in this patient population where disease often invades the trachea, esophagus, and great vessels. Patients undergoing potent antiangiogenic drug treatment should be warned about these potential risks (3). In Japan, lenvatinib is the only treatment approved by the health insurance system, and we have reported its efficacy (4,5). Previous reports revealed lenvatinib treatment results, including patients previously treated with other agents (6,7). Another report revealed results with lenvatinib in combination with other drugs (8). Another report revealed the results of lenvatinib treatment with the primary tumor resected and the metastases targeted (9). Genomic analysis is time-consuming, ATC disease progression is rapid, and death may occur while waiting for the genomic analysis report. The American Thyroid Association guidelines recommend that genomic analysis should be performed first after diagnosis and a therapeutic drug should be the first choice of treatment if available (3). Thus, this study aimed to report lenvatinib outcomes as an initial and single-agent treatment in unresectable ATC of the primary tumor and examine its safety and efficacy. In addition, we reviewed the pathological findings in two cases in which conversion surgery was feasible after response to lenvatinib treatment and tumor shrinkage. Moreover, genomic analysis results indicated the extent to which a therapeutic drug for ATC might be found.

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Abbreviations: ATC, anaplastic thyroid cancer; IRB, Institutional Review Board; DTC, differentiated thyroid cancer; BSC, best supportive care; PTX, paclitaxel; eGFR, estimated glomerular filtration rate; PFS, progression-free survival; OS, overall survival; AE, adverse events; CI, confidence intervals; CGP, comprehensive genomic profiling; FFPE, formalin-fixed paraffin-embedded; FMI, Foundation Medicine Inc.; TNM, Tumor, Node, Metastasis (a cancer staging system); AJCC, American Joint Committee on Cancer; PR, partial response; TMB, tumor mutational burden; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; RAI, radioactive iodine; EZR, Easy R (statistical software)

Key words: ATC, lenvatinib, retrospective study, genetic analysis

Materials and methods

Patients. The study was approved by our Institutional Review Board (IRB), Kanagawa Cancer Center (Yokohama, Japan) and each patient signed a comprehensive consent form and a treatment consent form. This single-institution, retrospective cohort study evaluated 81 patients who were diagnosed with ATC and treated in the Kanagawa Cancer Center, Japan from April 1, 2011 to July 31, 2022. Eligible patients were aged >20 years, had at least one measurable target lesion, and had pathologically confirmed ATC. The pathological review was performed by three pathologists with experience in thyroid pathology. This study protocol was reviewed and approved by our IRB (#2019-34). Of the 81 cases of ATC in our department, four with possible radical surgery upon initial diagnosis, 12 with metastases that turned into ATC, and nine with anaplastic transformation during lenvatinib treatment in differentiated thyroid cancer (DTC) were excluded from the study. Hence, this study included 56 patients with unresectable primary ATC. From 2011 to 2015, 12 patients were treated with weekly paclitaxel (PTX), 36 patients were treated with lenvatinib after 2015, and eight patients, who refused drug treatment, were treated with best supportive care (BSC). All patients were histopathologically diagnosed as ATC by biopsy or surgery. This study is a retrospective cohort study.

Drug treatment. Lenvatinib was started at 24 mg and PTX at 80 mg/m² weekly (10). The starting dose of lenvatinib was reduced for patients with diabetes and/or hypertension, >80 years, weighed <40 kg, with chronic kidney disease, or were poorly controlled. In addition, doses were reduced or withdrawn during treatment depending on the patient's condition. The actual lenvatinib treatment was performed as reported according to DTC (11). Renal function was evaluated by estimated glomerular filtration rate (eGFR), and the treatment was withdrawn when the eGFR was <30 ml/min/1.73 m².

Efficacy. Time to treatment failure, progression-free survival (PFS), and overall survival (OS) in the lenvatinib and PTX groups were performed by the log-rank test. We evaluated the response rate according to Response Evaluation Criteria in Solid Tumors (12) version 1.1 (13). A spider plot of the change in maximum tumor diameter from the start of treatment to the time of clinical progressive disease was shown in the lenvatinib treatment group. The time of best response was determined based on these results. Comprehensive genomic profiling (CGP) was performed on cases after 2019 when insurance reimbursement became available. Formalin-fixed paraffin-embedded tissue sections (FFPE specimens) of biopsy or surgical specimens performed at diagnosis were submitted to Foundation Medicine Inc. (FMI) for testing and analyzed for 324 cancer-related genes.

Safety and tolerability. Safety parameters, including adverse events (AE), hematology and clinical chemistry, urinalysis, vital signs, and electrocardiograms, were assessed at the baseline and every visit during the follow-up. AEs were graded from 1 to 5 according to the Common Terminology Criteria for Adverse Events version 5.0 (<http://www.jcog.jp/doctor/tool/ctcae5.html>), and the maximum value was totaled for each patient.

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Statistical analysis. Statistical analyses were performed using the EZR version 1.37 (<https://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/download.html>). The Fisher's exact test was used to analyze nominal variables, whereas the Kruskal-Wallis test was used to assess continuous variables. Continuous variables are presented as medians with their 95% confidence intervals (CI), and categorical variables are presented as numbers with percentages. The Kaplan-Meier method in conjunction with the log-rank test was used to analyze the OS curve. Univariate regression analysis, with calculated hazard ratios and their 95% CI, was used to identify the clinical features associated with PFS and OS. All P-values were two-sided, and P<0.05 were considered statistically significant.

Results

Treatment outcomes. Two cases are currently alive, whereas 54 have died. The mean survival was 4.34 months. Table I compares patient backgrounds in the lenvatinib, PTX, and BSC treatment groups. No significant differences were found in age, gender, weight, or TNM staging (AJCC Cancer Staging Manual 8th Edition, 2017). In addition, no significant differences were found in the percentage of radiotherapy intervention, lung metastases, and maximum tumor size. Survival was significantly longer in the lenvatinib group, averaging 5.8 months (P=0.004). The PTX and BSC groups survived 1.98 and 1.20 months, respectively.

Table II shows the results of the 36 lenvatinib-treated patients with the best response. The mean starting dose and treatment duration was 20.2 mg and 4.89 months, respectively. Median PFS was 3.5 months (95% CI: 2.3-5.37). In contrast, the PTX group revealed no cases of PR, and the mean duration of treatment was 1.65 months.

Fig. 1 shows the comparison of OS between the lenvatinib and PTX groups. The median OS was 4.77 and 2.07 months in the lenvatinib and PTX groups, respectively, indicating a significant survival benefit (P=0.0000163).

Adverse events of lenvatinib. The average lenvatinib treatment duration was 4.89 months, and Fig. 2 graphically depicts the AEs that appeared during that time. The most common AE was hypertension, which occurred in 29 (80.6%) patients, but there were no Grade 3 or higher AEs that would interfere with continued treatment. The next most common AEs were loss of appetite in 18 (50.0%), cavitation in 17 (47.2%), proteinuria and fatigue in 15 (41.7%), necrosis in 14 (38.9%), cutaneous fistula in 12 (33.3%), and tracheal fistula (including pharyngoesophageal fistula) in 9 (25.0%), and hand-foot syndrome in 8 (22.2%) patients. Necrosis was observed in two patients, who died of hemorrhage from the common carotid artery. Two patients had Grade 3 loss of appetite and one had a gastrointestinal hemorrhage, of whom treatment was discontinued and the patient was treated with BSC.

Progress of the treatment. Surgical tracheotomy was performed upon initial presentation to avoid asphyxia or for local control in five cases in the lenvatinib group and in three cases in the other treatment groups, all of which were

Table I. List of patient background in lenvatinib, paclitaxel and best supportive care treatment groups.

Factor	Treatment			P-value
	BSC	Lenvatinib	PTX	
N	8	36	12	
Age, years	74.75 [62,87]	72.33 [47,85]	72.75 [61,86]	0.812
Sex (%)				1.000
Female	5 (62.5)	19 (54.3)	7 (58.3)	
Male	3 (37.5)	16 (45.7)	5 (41.7)	
PS (%)				
0	3 (37.5)	27 (75.0)	9 (75.0)	0.064
1	4 (50.0)	9 (25.0)	2 (16.7)	
2	1 (12.5)	0 (0.0)	1 (8.3)	
Stage (%)				0.864
IVB	1 (12.5)	7 (19.4)	1 (8.3)	
IVC	7 (87.5)	29 (80.6)	11 (91.7)	
Lung metastasis (%)	7 (87.5)	29 (80.6)	11 (91.7)	0.864
Radiation therapy (%)	0 (0.0)	9 (25.0)	1 (8.3)	0.228
Body weight, kg	47.00 [40,58]	56.27 [41,88]	51.29 [37,70]	0.0934
Maximum diameter, mm	56.79 [37,85]	48.78 [24,92]	57.29 [30,92]	0.177
Overall survival, months	1.20 [0.3,2.2]	5.83 [0.5,28.9]	1.98 [0.2,4.9]	0.0000264 ^a

^aP<0.05. The data were subjected to statistical analyses using appropriate methods. The Fisher's exact test was applied to analyze nominal variables, whereas Kruskal-Wallis test was used for continuous variables. Continuous variables are indicated using median and range [minimum and maximum]. TNM staging was performed using the 8th edition of the AJCC staging system for thyroid cancer (AJCC-8). BSC, best supportive care; PTX, paclitaxel; AJCC, American Joint Commission on Cancer.

Table II. Comparison of lenvatinib and paclitaxel outcomes.

Factor	Lenvatinib	PTX
N	36	12
ORR		
Partial Response (%)	12 (33.3)	0
Stable disease (%)	19 (52.8)	6 (50.0)
Progressive disease (%)	4 (11.1)	3 (25.0)
Not evaluated (%)	1 (2.8)	3 (25.0)
Mean starting dose, mg (SD)	20.2 (4.7)	- ^a
Mean duration of treatment, months (SD)	4.89 (5.0)	1.65 (1.3)

^aPTX (80 mg/m²) was continued weekly until PD. PTX, paclitaxel; ORR, overall response rate; SD, standard deviation; PD, progressive disease.

resectable and positive for margins. Conversion surgery was possible in two cases, and their histopathological images are shown in Fig. 3. No residual tumor was observed on gross examination in both cases; however, histology demonstrated positive margins. Fibrosis without necrosis and viable tumor cells were found in the tumor in case A and localized tumor necrosis was found in case B; however, both specimens showed residual viable cells. Local tumor necrosis was observed in case B; however, both specimens showed residual viable cells.

Radical surgery was impossible although lenvatinib treatment reduced the tumor size.

Fig. 4 shows the evolution of the maximum tumor diameter after lenvatinib treatment. The plots are shown until the final image evaluation at the end of treatment. Tumor shrinkage is observed within 1-2 months of treatment in most cases. Thereafter, treatment is maintained at the current level and discontinued at 4 months. The longest period of imaging evaluation is 9 months.

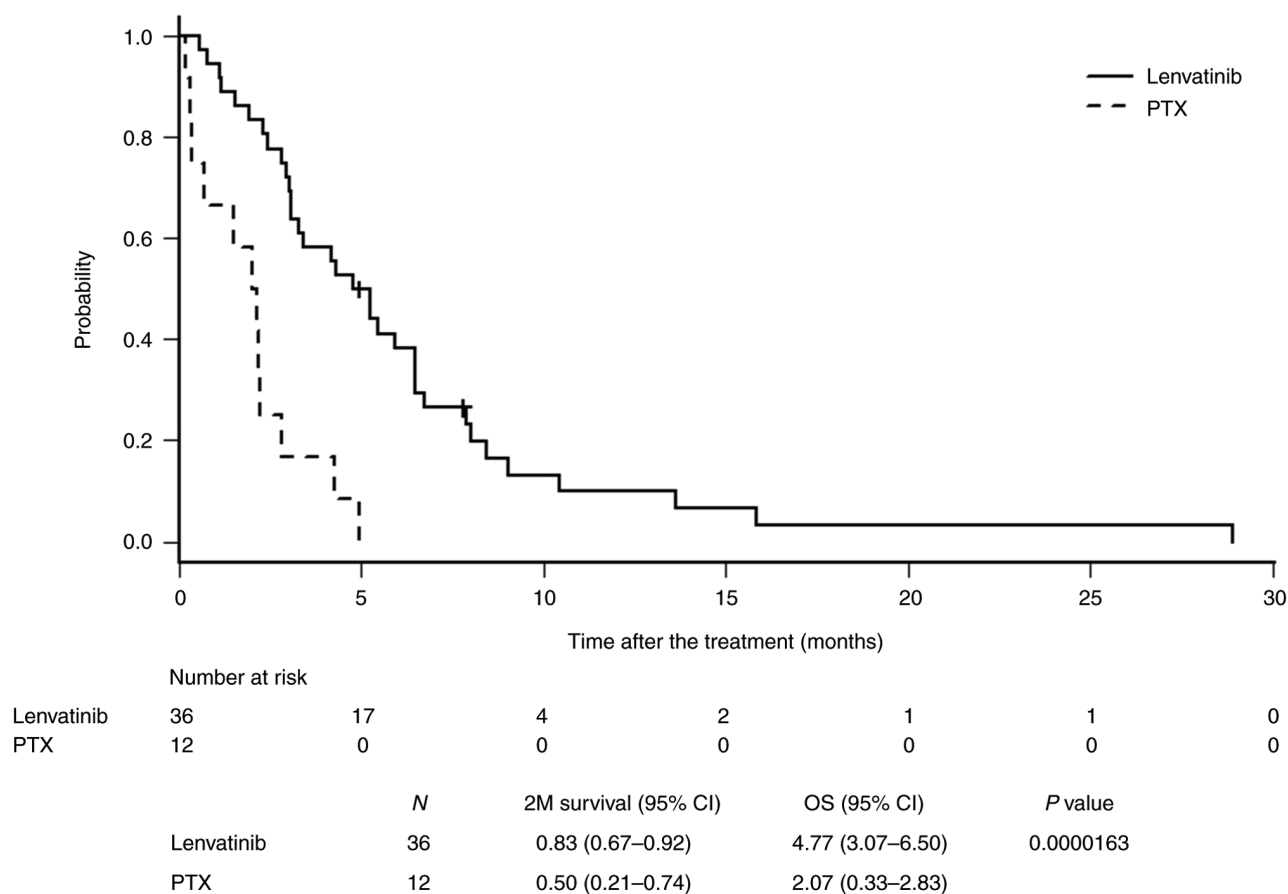


Figure 1. OS comparison between lenvatinib and PTX treatment. Survival curves of 36 patients treated with lenvatinib and 12 patients treated with PTX were compared. The black line represents the lenvatinib group and the dotted line represents the PTX group. The 2-month survival rate in the lenvatinib-treated group is 83, and 50% in the PTX-treated group. The median OS was 4.77 months in the lenvatinib group and 2.07 months in the PTX group, indicating a significant survival benefit ($P=0.0000163$). PTX, paclitaxel; OS, overall survival.

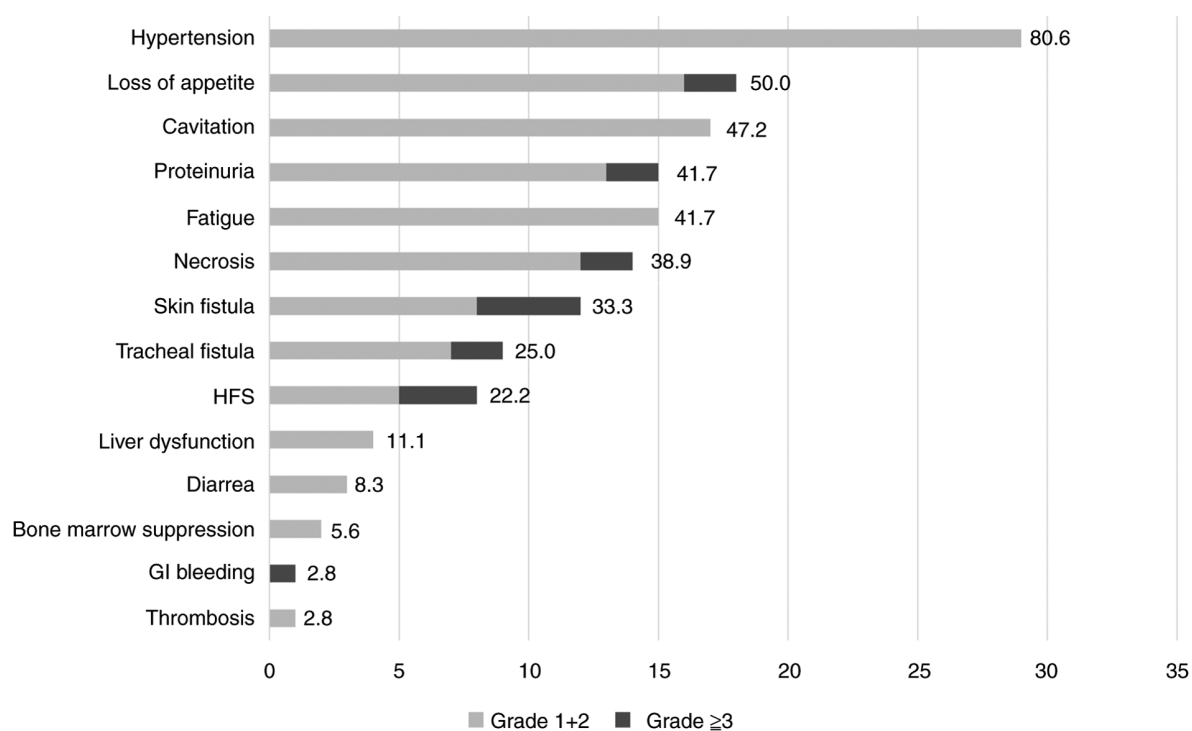


Figure 2. AEs recognized lenvatinib treatment for ATC. Among the AEs that appeared, the light gray bar indicates grades 1 and 2, and the dark gray bar indicates grades 3 or higher, in decreasing order of frequency as a stacked bar graph. All grade AE frequencies were displayed in % next to the bar. ATC, anaplastic thyroid cancer; AE, adverse event.

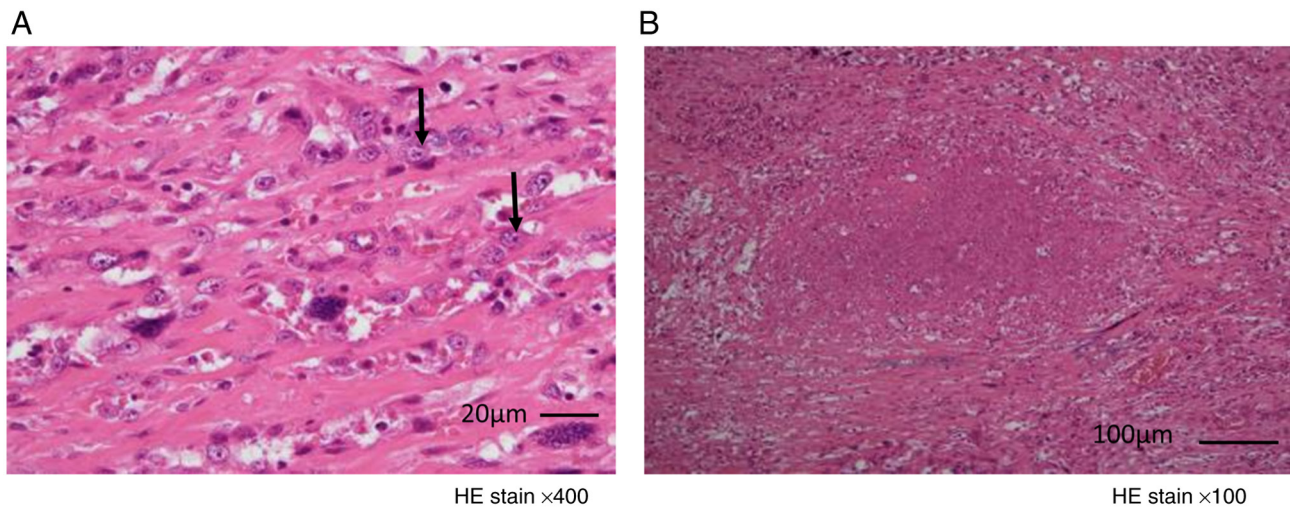


Figure 3. Histopathology of two cases in which surgical intervention was possible. (A) There was fibrosis without necrosis in the tumor and viable tumor cells are also present. Black arrows indicate viable ATC cells with large nuclei (HE staining x400). (B) There was localized tumor necrosis and there are viable tumor cells around it (HE staining x100). ATC, anaplastic thyroid cancer; HE, Hematoxylin and eosin.

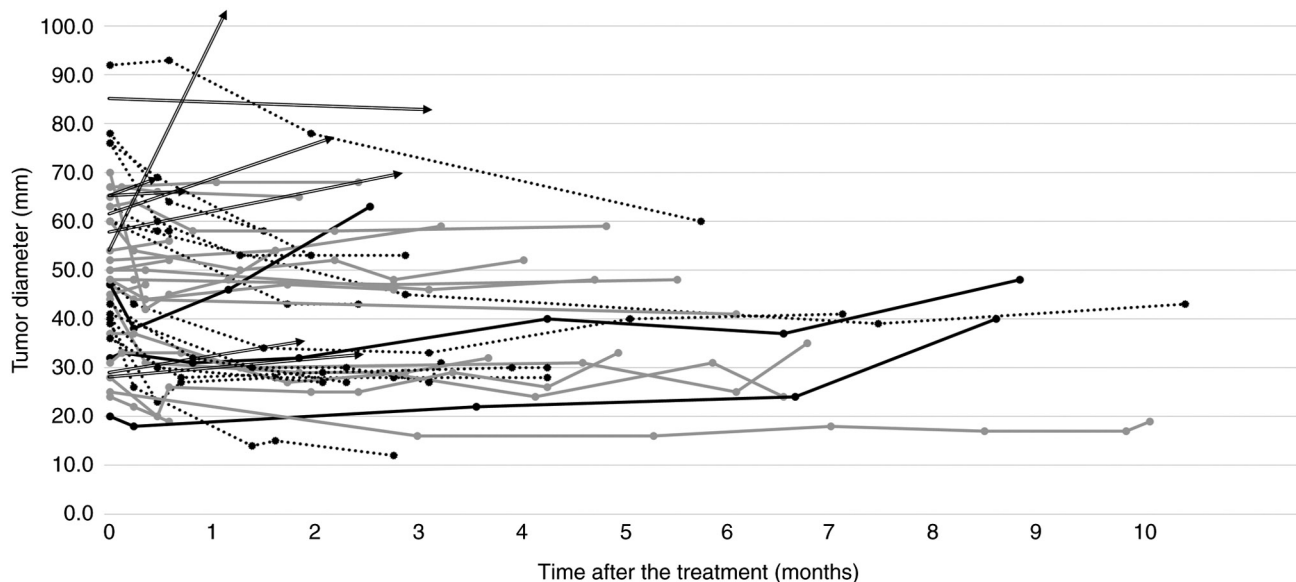


Figure 4. Changes in the maximum tumor diameter after lenvatinib and paclitaxel treatment. Line types were separated from baseline and final values. Dotted lines indicate PR, gray indicates SD, and black indicates PD. The cases treated with paclitaxel are represented by double lines and arrows. In most cases, tumor shrinkage is observed within 1-2 months of treatment; thereafter, treatment is maintained at the current level and discontinued at 4 months. The longest period of imaging evaluation is 9 months. PR, partial response; SD, stable disease; PD, progressive disease.

Genomic profiling. CGP results are summarized in Table III for the major cancer-related gene abnormalities. All genetic abnormalities we observed are included in Table SI. The CGP results of 14 patients with ATC showed that 7 (50.0%) had *BRAF* mutation, 4 (28.6%) had *NRAS* mutation, 11 (78.6%) had *TERT* mutation, and 10 (71.4%) had *TP53* mutation. They were the most frequent mutations. These ATC cases 1-7 have *BRAF* mutations and can be treated with *BRAF* inhibitor drugs. Case 8 has *RET/PTC* fusion and can be treated with Selpercatinib. Case 3 has a high TMB and can be treated with Pembrolizumab. These are thought to be of PTC origin, which is consistent with the coexistence of PTC in the surgical specimens in cases 1-3 and in biopsy tissue in case 7. Cases 9-12 are more likely to be of FTC origin due to *NRAS* mutations, yet

cannot be ruled out because PTC also has *NRAS* mutations, although less frequently. Cases 9-14 have no available drugs.

Discussion

In the studies conducted by Wirth *et al* (6) and Higashiyama *et al* (7), the prior usage of anticancer medications was reported to be 70 and 40.5%, respectively. However, what distinguishes this current study is that it exclusively involves treatment-naïve participants, all experiencing their initial disease onset. The median PFS and OS were 2.6 months (95% CI: 1.4-2.8) and 3.2 months (95% CI: 2.8-8.2), respectively, which may not be an effective ATC treatment. Lenvatinib treatment resulted in disappointing survival for patients with

Table III. Summarized results of genetic analysis of anaplastic thyroid cancer.

Gene abnormality ^a	Case no.													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
<i>BRAF</i>	1	1	1	1	1	1	1	0	0	0	0	0	0	0
<i>NRAS</i>	0	0	0	0	0	0	0	0	1	1	1	1	0	0
<i>RET/PTC</i> fusion	0	0	0	0	0	0	0	1	0	0	0	0	0	0
<i>TERT</i>	1	1	1	1	1	0	1	1	1	1	1	1	0	1
<i>TP53</i>	0	0	0	1	1	1	1	1	1	1	1	1	1	0
<i>PIK3CA</i>	0	0	1	0	0	0	1	0	0	0	0	1	0	0
<i>CDKN2A/2B</i>	0	0	1	1	0	0	0	1	0	0	0	0	1	0
<i>FGF</i>	0	0	0	0	0	1	0	0	0	0	0	0	1	0
<i>TMB high</i>	0	ND	1	0	0	0	0	0	0	0	0	0	0	0
<i>PTEN</i>	1	0	0	0	0	0	0	0	0	0	0	0	0	0

^aGene abnormalities i.e. variation or mutation, etc. in the 10 most frequent genes. 1, detect gene abnormality; 0, no abnormality; ND, not detectable. Due to the large volume and raw nature of the CGP data, a condensed representation of the data are presented as Table SI.

unresectable ATC. None of the results were satisfactory. A report describing the treatment results of distant metastases in ATC in which the primary lesion was resected (14) was shown in relatively good results. The median PFS and OS were 7.4 months (95% CI: 1.7-12.9) and 10.6 months (95% CI: 3.8-19.8), respectively, and the objective response rate was 24%. This report revealed that not all of the distant metastases have been pathologically proven to be ATC. ATCs, in which at least the primary tumor can be resected, have a better prognosis than unresectable cases. Another real-world report (9) included patients with previously treated cases or target lesions that include distant metastases. The number of patients is small, but this is the only study that investigated the effect of initial lenvatinib treatment, pathologically proven, unresectable ATC only. Median PFS and OS were 3.5 and 4.7 months, respectively. The result was slightly better than (6). This may be because patients were initially treated. However, CR with lenvatinib alone is not possible considering the pathology of the two cases of conversion surgery, and external irradiation or other drug therapy must be sequentially added postoperatively. ATC requires additional treatment, unlike the previously reported conversion surgery for DTC, because residual lesions can quickly enlarge and affect surrounding organs. This is not surprising given the much lower frequency of CR in studies of lenvatinib for RAI-refractory DTC (15).

The frequency of AEs themselves is less than reported for DTC because of the short administration duration in terms of safety (11). Grade 3 or higher fistulas (cutaneous and tracheal fistulas) were observed in three patients, and necrosis was observed in two patients, who died of hemorrhage. In addition, two cases had Grade 3 loss of appetite and one case had gastrointestinal bleeding. Eight of these patients (21.1%) could not continue lenvatinib treatment due to serious AEs. In contrast, 30 (78.9%) patients were able to continue treatment until they recognized progressive disease. The most clinically serious AEs of lenvatinib are fistula formation, rapid necrosis, and hemorrhage, as previously reported (4,5). Two deaths due to hemorrhage were caused by fistula formation and aseptic

abscess from necrosis, and local washing and continuous lenvatinib treatment in the hope that the tumor would shrink. Cutaneous fistulas are often fistulized at the site of needle biopsy. Lenvatinib treatment can be continued if the fistula is localized to the superficial skin, but lenvatinib should be immediately discontinued if there is a risk of tracheal or esophageal fistula and bleeding. Thus, we believe that safety can be assured by carefully monitoring local findings once lenvatinib therapy is initiated and preventing serious fistulas or bleeding events.

There are more numerous reports of CGP results (16), but our results revealed a high number of *BRAF* mutations, which are PTC-derived ATCs, indicating many PTC-derived ATCs, and FTC-derived ATCs inheriting *RAS* mutations and *de novo* ATC, all of which are consistent with previous reports. In addition, the high prevalence of *TP53* and *TERT* abnormalities as comorbid genetic abnormalities is consistent with previous reports (17). Results of drugs targeting the driver gene have been reported (18,19). Another study reported the combination with immune checkpoint inhibitors (8). These drugs could not be used in Japan because it was not reimbursed by health insurance. Therefore, this was a single-agent study of lenvatinib, but it is significant as real-world data. The median PFS was 3.7 months, indicating an effective treatment to halt disease progression for a little more than a month before the CGP results are known. Patients with *BRAF* mutations should be treated with *BRAF* inhibitors. Some reports are in combination with an immune checkpoint inhibitor. A study of 36 ATCs, including distant metastases, reported good results with median PFS and OS of 6.7 and 14.5 months, respectively (20). Drugs for *RAS* mutations may be applied or drugs targeting other driver genes may be developed in the future.

Lenvatinib treatment became available in 2015 and CGP testing became available in 2019, so there is a bias in which possible treatments and tests are selected depending on the timing of availability, and the limitation of this study is that it is not a random trial. Before 2015 in Japan, paclitaxel was

the only approved treatment for malignant thyroid tumors. However, since 2015, Lenvatinib has been specifically approved for treating anaplastic thyroid cancer. As a result, the choice of treatment options in this clinical research was constrained by considerations of insurance approval. This limitation has, in turn, potentially narrowed the scope of the study.

We evaluated the efficacy of lenvatinib in 36 patients with ATC with primary target organs. The response rate was 33%, and the median OS was 4.77 months. A safety review indicated that lenvatinib should be used under the careful observation of local findings. Two patients, who showed a reduction with lenvatinib, underwent conversion surgery, which prolonged the prognosis in terms of avoiding AEs, such as asphyxia, fistula, and hemorrhage due to tumor growth. However, the resection specimens were positive for margins, and CR was not possible even if the reduction was observed. At present, a treatment strategy of obtaining CGP results while the initial drug lenvatinib remained effective and lead to effective drug therapy is appropriate.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HI and ST designed the study. AT analyzed the data. HI, ST, AT and KM contributed by performing the surgery and caring for the patients. ST and KM confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The chemotherapy committee of Kanagawa Cancer Center approved this regimen of lenvatinib for use in patients with ATC. The cancer board of the hospital also approved lenvatinib treatment, including surgery, for patients with ATC. Written informed consent was obtained from all participants. All experimental protocols were approved by the Institutional Review Board of Kanagawa Cancer Center (approval no. #2019-34). We confirmed that all methods were conducted in accordance with relevant guidelines and regulations.

Patient consent for publication

All patients provided written informed consent prior to their treatment. This form indicated that their personal data could

be utilized for academic or paper presentations, with the assurance of maintaining absolute anonymity.

Authors' information

HI is an endocrine surgeon working at the Kanagawa Cancer Center and has extensive experience in several surgeries for ATC, as well as ATC treatment.

Competing interests

The authors declare that they have no competing interests.

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