

Lenvatinib as a novel treatment for anaplastic thyroid cancer: A retrospective study

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Abstract. Anaplastic thyroid cancer (ATC) is associated with an extremely poor prognosis and is resistant to the majority of chemotherapies. In 2015, lenvatinib was approved for treating ATC in Japan. The present study aimed to evaluate the overall survival (OS) of patients with ATC treated with lenvatinib. A total of 23 patients with a definitive histological diagnosis of ATC who were treated at Kanagawa Cancer Center (Yokohama, Kanagawa, Japan) were enrolled. Surgical treatment was possible in 10 patients (including one debulking surgery), and lenvatinib treatment was postoperatively started. The remaining 13 patients were not eligible for debulking surgery; thus, lenvatinib was promptly approved as a life-saving treatment. The therapeutic effect was determined according to the Response Evaluation Criteria In Solid Tumors criteria (ver.1.1). The patients exhibited a lenvatinib response rate of 17.4% and a disease control rate of 43.5%. However, lenvatinib was associated with a 100% incidence of treatment-related adverse events (AEs), with hypertension being the most common AE (91.3%). Additionally, dose interruptions and reductions were required due to the development of tumor fistulas or other tumor-related AEs, and 9 (39.1%) patients discontinued treatment due to grade 3 or higher AEs.

The median OS time was 166 days. Overall, the present study demonstrated the effectiveness of lenvatinib against ATC, which is often chemotherapy-resistant. Successful treatment of fistulas developing due to tumor necrosis at the site of the primary lesion is crucial for improving the patient outcome. The response to lenvatinib in patients with ATC varies on a case-by-case basis and requires further investigation in future studies.

Introduction

Anaplastic thyroid cancer (ATC) is rare, representing only 1-2% of all thyroid cancer cases (1); however, it accounts for up to 50% of all thyroid cancer-related mortalities (2). ATC is more common in the elderly, and it almost always develops from a pre-existing well-differentiated thyroid cancer (3,4). The prognosis of ATC is extremely poor, with a recorded median survival time from diagnosis of ~4 months and a 1-year survival rate of ≤20% (5,6); furthermore, an analysis of 516 cases using the US Surveillance, Epidemiology and End Results database showed the median survival time to be 3 months and the 1-year survival rate to be 19.3% (3). Even in patients treated with a combined modality of surgery and chemotherapy, the 2-year survival rate is poor (7). The survival rate of patients with ATC has not changed over the past 20 years (8). Furthermore, it is unclear whether a comprehensive therapy, including chemotherapy and radiotherapy, followed by palliative surgery, will improve the prognosis in all patients. Sorafenib was approved for clinical use in 2014 for treating Iodine-131 refractory differentiated thyroid cancer (DTC), but not for anaplastic cancer; certain investigators supported regulatory approval of lenvatinib for treating unresectable thyroid cancer in Japan (9). In 2015, the Japanese Ministry of Health, Labor and Welfare approved the clinical use of lenvatinib for treating patients with ATC and DTC; this drug is now commercially available there for the same purpose. Lenvatinib is a multi-tyrosine kinase inhibitor (TKI) that targets vascular endothelial growth factor (VEGF) receptors 1-3, fibroblast growth factor (FGF) receptors 1-4, platelet-derived growth factor receptor- α , and the ret proto-oncogene and KIT proto-oncogene receptor tyrosine kinase (10). In a preclinical study, lenvatinib demonstrated antitumor activity in mouse ATC xenograft models (11).

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Abbreviations: AE, adverse event; ATA, American Thyroid Association; ATC, anaplastic thyroid cancer; BW, body weight; DCR, disease control rate; DTC, differentiated thyroid cancer; FGF, fibroblast growth factor; ORR, overall response rate; OS, overall survival; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; TKI, tyrosine kinase inhibitor; TTF, time to treatment failure; VEGF, vascular endothelial growth factor

Key words: anaplastic thyroid cancer, lenvatinib, overall survival, disease control rate, retrospective study, safety and efficacy

In addition, the aforementioned phase 2 study reported the safety and efficacy of lenvatinib in 17 patients with ATC, with a median progression-free survival time of 7.4 months [95% confidence interval (CI), 1.7-12], a median OS time of 10.6 months (95% CI, 3.8-19.8) and an objective response rate of 24 (9). We previously reported a minor series study on lenvatinib for 7 patients with ATC in 2017 (12). We reported that the response rate was 43%, and the disease control rate was 57% under the limitation of a short follow-up period and evaluating only the highest response of lenvatinib for ATC.

The present study reports the response rate of 23 patients with ATC to lenvatinib. The aim of the study was to assess the safety and efficacy of lenvatinib in patients with stage IVC ATC (Tumor-Node-Metastasis staging system 8th edition) (13). Furthermore, the management of severe adverse events (AEs) associated with lenvatinib use in order to maximize the benefits obtained from this TKI treatment is discussed.

Materials and methods

Patients. The present study was a retrospective study analyzing the clinical data from 23 patients with unresectable and pathologically confirmed ATC who were treated at Kanagawa Cancer Center (Yokohama, Kanagawa, Japan) between April 2015 and March 2017. Patients diagnosed with stage IVC ATC and treated with lenvatinib were included, while those who had been treated with other anticancer agents prior to using lenvatinib were excluded. Patients who could not take oral lenvatinib due to ATC-related dysphagia were also excluded. A total of 2 patients were initially diagnosed with stage IVB disease, but once distant metastasis was confirmed during surgery, IVC was diagnosed, and the patients were registered in the study. No stage IVA patients were encountered during the enrollment period. A total of 8 patients underwent surgical resection for the primary tumor prior to lenvatinib treatment in order to prevent extensive spread to the nearby important organs, including the air tract, esophagus and common carotid artery, and 2 patients underwent tumor volume reduction and prophylactic tracheotomy. The remaining 13 patients were not eligible to undergo any surgical treatment. A study was thus performed on whether lenvatinib can be considered a novel orphan drug for patients with ATC that cannot be otherwise treated.

Overall, 19 patients received lenvatinib at a daily dose of 24 mg/day, while the remaining 4 patients started it at daily doses of 20 mg (1 patient), 14 mg (2 patients) and 10 mg (1 patient) due to low body weight (BW) and poor performance status. The median duration of treatment was 5.4 months (range 0.4-27.9 months). Dose interruptions and incremental reductions in the dose (to 20, 14 or 10 mg/day) were permitted in case of toxic effects. The chemotherapy committee of the hospital approved the lenvatinib regimen, and the patients individually signed consent forms following adequate explanation of the treatment.

The study population comprised 15 women and 8 men (median age, 77.0 years; age range, 42-89 years). The tumor size was 44.2 ± 17.8 mm (median \pm standard deviation), with a 25th percentile of 29.0 mm and a 75th percentile of 58.5 mm. The median \pm SD of BW was 55.6 ± 12.2 kg, with a 25th percentile of 46.6 kg and a 75th percentile of 59.3 kg. Patient characteristics are summarized in Table I.

Evaluation. The radiological response to the TKI therapy was classified on the basis of the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 criteria (14) as follows: Complete remission (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Safety was assessed according to the National Cancer Institute Common Toxicity Criteria version 3.0 (15). In order to evaluate safety, the occurrence of any AE (grade 3-5) and the time for treatment discontinuation were recorded. Disease control rate (DCR) was defined as the percentage of patients who had CR, PR or SD. The assessment of the response evaluation was based on the RECIST criteria evaluated 1, 2 and 3 months post-treatment, with ≥ 4 weeks of response persistence. This continued until the final follow-up date or mortality without an end point or best response. The administration period for patients in whom the treatment was discontinued is graphically shown in Fig. 1 as the time to treatment failure (TTF) together with the reason for discontinuation.

Statistical analysis. Overall survival (OS) was defined as the time elapsed between the dates of the first treatment and mortality. Kaplan-Meier estimator on the SPSS software (version 24; IBM Corp., Armonk, NY, USA) was used to calculate OS and applied the log-rank test. $P < 0.05$ was considered to indicate a statistically significant difference. To verify the efficacy of lenvatinib, the OS times of patients who were treated with surgery first and of those who were treated with lenvatinib only were also calculated. Efficacy analysis of OS was summarized by the Kaplan-Meier method using median time with 95% confidence interval (CI).

Results

Patients. The proportion of patients who received lenvatinib and experienced treatment-related AEs was 100%. The most common AE was hypertension (21/23, 91%). Other common AEs were general fatigue and anorexia (15/23, 65%), proteinuria (14/23, 61%) and tumor-skin fistulas (6/23, 26%). The majority of the AEs, with the exception of the tumor fistulas, could be controlled with medication. The individual progress of the patients has been graphically presented with a swimmer plot in Fig. 2. Patients with tracheal fistulas are shown in Fig. 3, and representative images of the fistulas are shown in Fig. 4.

A total of patients (patient nos. 1, 6, 7 and 9) exhibited a PR, 6 patients (patient nos. 2, 4, 11, 13, 16 and 19) experienced SD and 4 patients (patient nos. 5, 12, 14 and 18) developed new lesions (3 brain metastases and 1 liver metastasis) that were eventually considered PD. In addition, 3 patients (patients 3, 15 and 17) exhibited PD. The remaining 6 patients (patient nos. 8, 10 and 20-23) were not evaluated, as they could not undergo examinations at 1-month intervals and were designated as non-evaluable. A total of 9 (39%) patients discontinued the treatment due to treatment-related AEs that were grade 3 or higher. These 9 patients succumbed within 1 month of the cessation of the lenvatinib, an indication of the aggressiveness of the ATC. The treatment in 2 patients was resumed following healing of the tumor fistula or cavitation, and they exhibited a PR. A total of 19 patients discontinued the treatment, and they all succumbed; their TTFs are shown in Fig. 4. The reasons for treatment discontinuation were as follows: AEs, 9 patients; PD, 7 patients; and other reasons (sudden mortality, aspiration

Table I. Patient baseline clinical characteristics (n=23).

Characteristics	Value
Median age (range), years	77.0 (42-89)
Gender, n (%)	
Male	7 (30.4)
Female	16 (69.6)
PS, n (%)	
0	11 (47.8)
1	7 (30.4)
2	5 (21.7)
Site of metastasis, n (%)	
Lung	19 (82.6)
Bone	3 (13.0)
Others	9 (39.1)
Median size of tumor, mm ^a	44.2±17.8 (29.0-58.5)
BW, kg ^a	55.6±12.2 (46.6-59.3)
Median initial dose, mg ^a	21.9±4.3 (24-24)
Median ongoing dose, mg ^a	11.5±3.0 (9.5-14)

^aParameters listed as mean ± standard deviation (interquartile range). BW, body weight; PS, performance status.

pneumonia or treatment rejection by the patient), 3 patients. The median TTF was 77 days (range, 11-837 days).

Efficacy. The overall response rate (ORR) was 17.4% and the DCR was 43.5% (Table II). The median OS time was 166 days. The OS time of the patients treated with surgery first was greater than that of the patients treated with lenvatinib only. The median OS time was 130 days (95% CI, 58-178) for patients treated with lenvatinib only, whereas it was 265 days (95% confidence interval, 73-478) for those treated with surgery first (Fig. 5). Although the survival curves for the two groups appeared to be different, there was no statistically significant difference between the groups (log-rank test, $P=0.07$).

Discussion

Current therapies for ATC have limited efficacy; when combined with other chemotherapies, a higher response rate (50%) can be achieved, but the duration of the response is often short (2-5 months) (16). A phase 2 trial (17) of paclitaxel in patients with ATC reported an ORR of 53%; another trial of carboplatin and paclitaxel in combination with fosbretabulin reported a non-significant increase in OS time (18). The median OS time was 5.2 months (95% CI, 3.1-9.0) for the CP/fosbretabulin arm [$n=55$; hazard ratio 0.73 (95% CI, 0.44-1.21)] and 4.0 months (95% CI, 2.8-6.2) for the CP arm ($n=25$; $P=0.22$ (log-rank test)). A phase 2 trial targeted ATC cases with recurrent masses observed following surgery or subsequent to any additional external irradiation (16); by contrast, the present study was fundamentally different from the aforementioned study, as it was a single-arm study for patients treated with lenvatinib alone. In addition, the researchers of the paclitaxel trial had to modify the

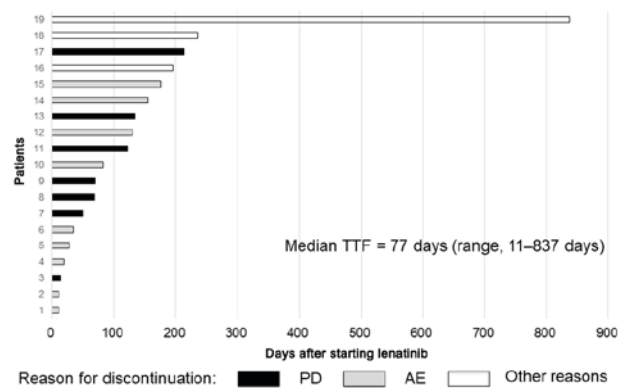


Figure 1. TTF for lenvatinib. The 7 black bars demonstrate PD, while the 9 gray bars demonstrate an AE as the reason for treatment failure. The other three white bars show other treatment failure reasons (sudden death, aspiration pneumonia and treatment rejection by the patient). TTF, time to treatment failure; AE, adverse event.



Figure 2. Swimmer plot graph showing clinical courses of patients with ATC treated with lenvatinib. The widest boxes indicate the initial high dose of lenvatinib, and the thinner boxes indicate dose reductions to 10-14 mg. Dotted lines indicate periods of interruption. Black triangles indicate discontinuation. S indicates surgical treatment. Stars indicate the time when a PR was diagnosed based on follow-up computed tomography images. Bold arrows indicate treatment continuation. X indicates mortality. Treatment assessment and cause of mortality are listed side by side. ATC, anaplastic thyroid cancer; PD, progressive disease; SD, stable disease; NE, not evaluable; GI, gastrointestinal; PR, partial response; BSC, best supportive care.

response criteria by decreasing the requirement of response persistence from 4 to 2 weeks due to quick disease progression. Although the ORR was 53%, the median survival of all patients following the diagnosis (25 weeks) was almost identical to that of patients in the present study (24 weeks). Given the poor prognosis, the American Joint Committee on Cancer staging system considers all patients diagnosed with ATC to have stage IV disease; subcategorization into stages IVA, IVB and IVC is based on whether the cancer is confined to the thyroid gland, has extra thyroidal extension or has metastasized to distant sites, respectively (19). Hence, as unresected ATC is almost certainly lethal, the American Thyroid Association (ATA) guidelines recommend that surgery be performed if technically possible and if not likely to cause any unacceptable morbidity (20). Stage IVA tumors are resectable, as intrathyroidal anaplastic tumors are

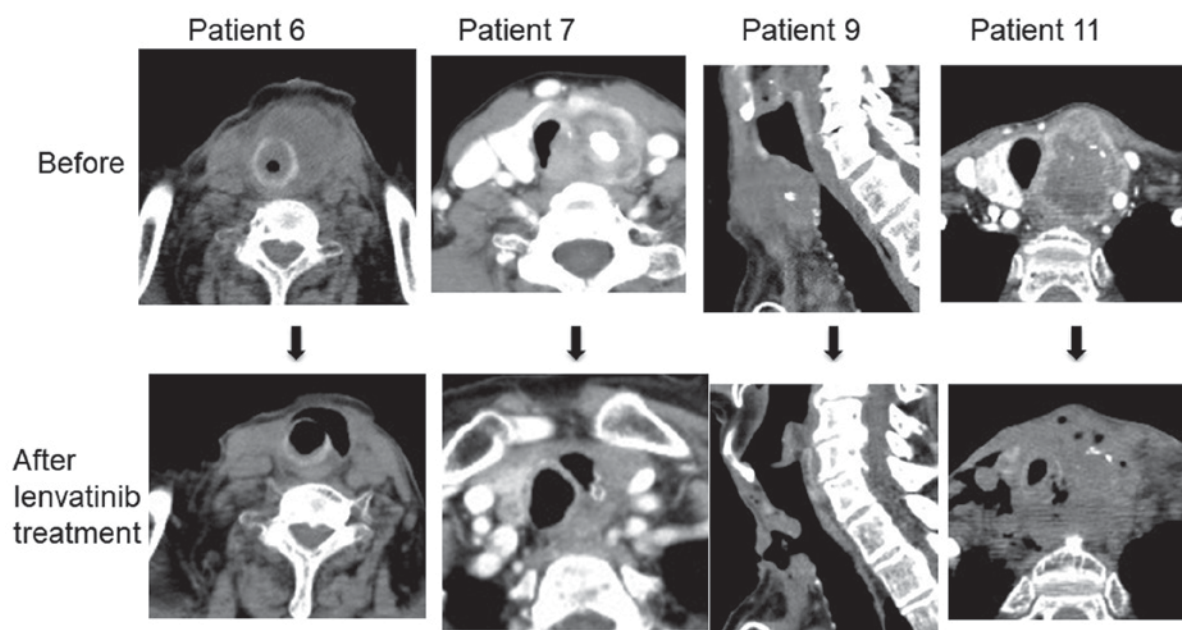


Figure 3. Tracheal fistulas in patient nos. 6, 7, 9 and 11. The fistulas in patient nos. 6 and 7 were localized, and treatment continuation was possible with dose reduction. Patient no. 9 exhibited a PR, but a skin fistula became a trachea-skin fistula on day 170 after the treatment initiation. Secretions from tumor necrosis flowed into the trachea and led to severe aspiration pneumonia and mortality. Patient no. 11 presented with metastatic spread to the surrounding soft tissues; the patient succumbed from subsequent mediastinitis.



Patient 1: Tumor regrowth through the tumor-skin fistula



Patient 22: Tumor-skin fistula and extensive necrosis surrounded the artery leading to grade 5 bleeding.

Figure 4. Tumor-skin fistula. Patient no. 1 developed a tumor-skin fistula on day 185 after the lenvatinib treatment initiation. The fistula was never cured during the lenvatinib treatment; finally, tumor re-growth was recognized through the fistula to the outside of the skin. Patient no. 22 developed a tumor-skin fistula 10 days after starting the treatment. Initially, the carotid artery was not involved, but then extensive necrosis surrounded the artery and lead to grade 5 bleeding. The direct exposure of the carotid artery to the fistula cavity likely contributed to the subsequent carotid blowout syndrome with torrential hemorrhage.

classified as stage IVA disease, while the presence of lymph node involvement or gross extrathyroidal extension without distant metastasis is classified as stage IVB. (21) Stage IVB tumors can be either resectable or unresectable depending on the expertise of the surgeon. However, Haigh *et al* (22) reported aggressive surgery to be worthwhile in selective cases when combined with chemotherapy and/or radiotherapy, even if some macroscopic disease was left behind to preserve organ function. The median survival rates in patients with stage IVA, IVB and IVC disease have been reported as 9.00, 4.80 and 3.02 months, respectively (23). Among the present

study patients, 9 underwent surgery prior to lenvatinib treatment. Surgery provides the advantage of securing the airway and preventing fistula formation when there is no residual tumor around the airway (22). OS time was compared in patients initially treated with surgery and in those treated with lenvatinib only. The surgery-first patients experienced a prognosis extension of 135 days compared with the median OS value; however, there was no significant difference between the surgery-first and lenvatinib-only groups. In patients who did not undergo surgery, fistula formation occurred in 6/14 patients (42.9%), and the fistula was difficult

Table II. Antitumor effectiveness of lenvatinib in patients with anaplastic thyroid carcinoma (n=23).

Response to lenvatinib	Patients, n (%)
Complete response	0 (0.0)
Partial response	4 (17.4)
Stable disease	6 (26.1)
Progressive disease	7 (30.4)
Not evaluable	6 (26.1)
Overall response rate	4 (17.4)
Disease control rate	10 (43.5)

to treat. According to studies that reported tumor fistulas in 2010 and 2011, frequent dose interruptions are required for patients receiving oral TKIs (sorafenib, sunitinib and/or lenvatinib) (24,25). Stage IVC ATCs were typically treated with systemic chemotherapy and/or radiation therapy or palliative care options prior to lenvatinib approval for clinical use in 2015 (2). Certain multicenter collaborative studies and trials on TKI treatment for ATCs have been published since then (9,26,27). Tahara *et al* (9) reported a phase 2 clinical trial and included only 6 (35%) patients with stage IVC ATC; the remaining patient population was comprised of 4 (24%), 5 (29%) and 2 (12%) patients with stage IVA, stage IVB and unknown stage ATC, respectively. Moreover, the patients previously underwent treatments, including surgery (n=14; 82%), chemotherapy (n=7; 41%) and radiation (n=9; 53%). The present study only targeted patients with stage IVC ATCs with extremely poor prognoses, and was designed as a single-arm study with lenvatinib as the first-line anticancer drug.

There are certain limitations to the present study, including the small sample size, the retrospective design, including bias and confounding factors, the lack of a comparator group, and the inability to generalize the results to other populations. Nevertheless, to the best of our knowledge, this is the first report on 23 patients treated with lenvatinib only for stage IVC ATC, and the results will provide useful data for future treatment studies. Based on these findings, it may be concluded that lenvatinib is a potential candidate for clinical trials with concomitant medicines in the future; for example, using a v-raf murine sarcoma viral oncogene homolog B1 (BRAF) inhibitor for treating a tumor with BRAF mutation should clearly provide good results (28). Also, to the best of our knowledge, the present study is the first to compare the results of lenvatinib and surgery among patients with stage IVC ATC in the same institution. Future studies should focus on demonstrating the benefits of lenvatinib as the standard treatment for stage IVC ATC, on how to decrease the incidence of AEs and on how to manage the severe AEs associated with lenvatinib use.

Regarding the most frequent AEs, hypertension, gastrointestinal symptoms and hand-foot syndrome may respond to oral medicines or Hirudoid Soft® Ointment 0.3% for skin disorders. In the present study, patients required a short-term interruption of lenvatinib for recovering from AEs, including proteinuria, fatigue, anorexia and thrombocytopenia. For managing more serious AEs, the present study describes our experience with tumor fistulas and lenvatinib-induced bleeding.

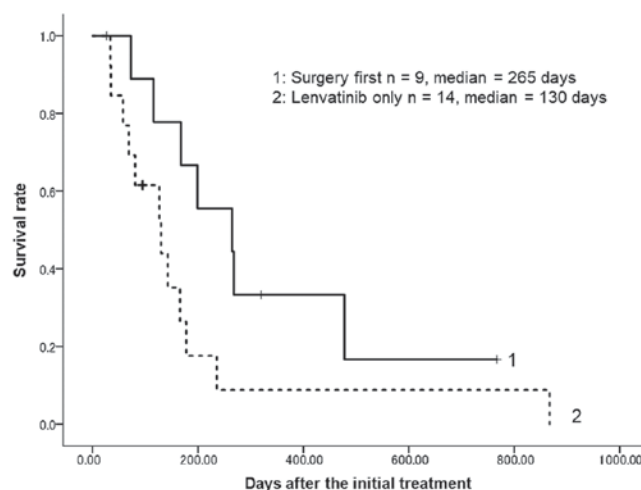


Figure 5. OS curves. A Kaplan-Meier estimator (SPSS software) was used to derive survival curves, which indicated the median OS time of patients treated with lenvatinib as being 166 days. The OS times of the patients treated with surgery first were longer than the OS times of others treated with lenvatinib only (shown for reference). The median OS time of patients treated surgically was 265 days and that of those treated with lenvatinib only was 130 days. OS, overall survival.

In the treatment of anaplastic carcinoma, the biggest problem is that the majority of patients present with unresectable primary tumors, and this may explain the development of necrosis or fistulas during lenvatinib treatment. Once a fistula develops, frequent dose interruptions are required to prevent the spread of the fistula (29). Recent guidelines published by the ATA discuss the management of the compromised airway in such patients, and suggest that a tracheotomy should be performed to secure the airway in circumstances of life-threatening airway obstruction (30). Airway compromise with a thyroid mass may be a presenting feature of ATC, or it may occur in a patient with a pre-existing diagnosis of the disease (30). Notably, patient nos. 8 and 10 in the present study (Fig. 2) underwent prophylactic tracheotomies to prevent later respiratory complications. However, their follow-up showed no benefit from the lenvatinib treatment. Each of these patients suffered from local wound healing complications, thus, treatment was discontinued and their OS times were significantly lower than those of other patients. The patients in the present study were ineligible for chemotherapy or radiation therapy, and their survival was estimated to be ~3 months (23) without lenvatinib treatment. The present study demonstrates that lenvatinib is of value as an orphan drug for stage IVC ATC. Although surgical resections of primary tumors lead to longer OS times even in the presence of distant metastasis, volume reduction surgeries and prophylactic tracheotomies complicate matters and make lenvatinib treatment difficult.

Patient no. 20 in the present study (Fig. 2) developed grade 4 gastrointestinal bleeding, and patient no. 22 developed grade 5 tumor bleeding during lenvatinib treatment. Tumor-skin fistulas were observed in 6 patients, and 1 patient (patient no. 22) experienced direct exposure of the carotid artery to the fistula cavity that likely contributed to the subsequent carotid blowout syndrome with torrential hemorrhage (24). The complete encasement of the artery whether by the tumor or necrotic tissues requires careful drug administration or dose interruptions. Vascular disruption by

inhibition of existing VEGF/VEGF receptor-dependent tumor blood vessels often leads to tumor necrosis and cavitation, and the same mechanism is likely to explain the protracted wound healing observed with lenvatinib use.

In conclusion, the present study assessed the treatment outcomes in 23 patients with unresectable ATC at a single institute and discussed the management of AEs associated with lenvatinib use. Generally, a DTC, even subsequent to recurrences and with distant metastases, is slowly progressive, whereas ATC exhibits an extremely poor prognosis, with chemotherapy overall being ineffective against it. Although lenvatinib showed a limited positive effect, it is associated with a high incidence of AEs, and this must be weighed against the benefits of the treatment. The successful treatment of fistulas developed due to necrosis is crucial for improving the treatment outcomes. Future investigations on VEGF or FGF expression in ATC should assist in optimizing the analyses for lenvatinib efficacy and for preventing treatment-related fatal AEs.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

HI, HY and NS designed the study. HT analyzed the data. HN checked analysis and interpretation data, especially statistical analysis. NS, HN, ST and KM contributed by performing the surgery and caring for the patients. ST and KM contributed to data acquisition. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The chemotherapy committee of Kanagawa Cancer Center (Yokohama, Kanagawa, Japan) 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. The study was approved by the Institutional Review Board of Kanagawa Cancer Center.

Patient consent for publication

All patients provided a comprehensive consent form stating that personal data could be used for academic presentation or paper presentation while ensuring complete anonymity prior to receiving the treatment.

Competing interests

The authors declare that they have no competing interests.

Authors' information

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

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