Treatment of anaplastic thyroid cancer with tyrosine kinase inhibitors targeted on the tumor vasculature: initial experience in clinical practice

Sae Ishihara *, Naoyoshi Onoda *, Satoru Noda, Yukie Tauchi, Tamami Morisaki, Yuka Asano, Shinichiro Kashiwagi, Tsutomu Takashima and Masaichi Ohira

Department of Breast & Endocrine Surgery, Osaka City University Graduate School of Medicine, Osaka 545-8585, Japan

Abstract. Anaplastic thyroid cancer (ATC) is a rarely occurring refractory disease. While recent clinical trials have demonstrated the efficacy of tyrosine kinase inhibitor (TKI) therapy for ATC, evidence is scarce in clinical practice. In this study, we reviewed our initial experiences with TKI treatment in ATC patients with the aim of revealing the efficacy and safety of the same in clinical practice. We retrospectively reviewed our experiences with TKI treatment use in ATC patients diagnosed at our institute from 2014 to 2019. Changes in the patients’ neutrophil-to-lymphocyte ratio (NLR) by TKI therapy introduction as well as their clinical factors to indicate the efficacy were examined. Seven patients showed no indication for TKI treatment, while 13 (65%) received treatment. The median duration of TKI treatment was 1.9 months. All patients died, and the overall survival period from diagnosis was 4.7 (95% confidence interval: 2.0–11.5) months. Adverse events ≥Grade 3 were observed commonly (92.3%), and resulted in the termination of TKI treatment in six cases (46.1%). Existence of multiple unfavorable characteristics (higher Prognostic Index) was associated with poor survival. The NLR decreased after the introduction of TKIs and increased again when treatment failed. The response rate to TKI among the ATC patients were approximately 30% in practice. Although the duration of the response was short, several patients demonstrated long survival durations when TKI treatment was provided after successful multidisciplinary treatment to control local disease. Decreases in high NLR values during treatment may suggest the continued effect of TKIs.

Key words: Anaplastic thyroid cancer, Tyrosine kinase inhibitor, Systemic therapy, Prognostic index, Neutrophil-to-lymphocyte ratio
fibroblast growth factor receptor [16]. However, adverse events associated with TKI use have been frequently reported in Japanese patients, such as those with hypertension, proteinuria, hand-foot syndrome, fatigue, and appetite loss [17]. Sometimes, these adverse events may impair patients’ quality of life or cause life-threatening events that may lead to treatment termination. Although recent clinical trials have demonstrated the efficacy of TKI therapy for ATC, evidence is scarce in clinical practice. Two reports have shown the treatment results of TKI for ATC in clinical practice [13, 18]. Still, no insight has been demonstrated concerning the indicator to prospect the prognoses or monitor the efficacy.

The prognostic index (PI) was designed to evaluate the prognoses of ATC patients [19] and has been confirmed reliable prospectively [20]. PI was, thus, listed in Japanese guidelines as a useful tool in determining appropriate therapeutic strategies [8]. This index was devised based on the number of four unfavorable characteristics the patient possessed which are as follows: 1) acute symptoms presenting within 1 month, 2) leukocytosis with a leukocyte level of 10,000/mm$^3$ or greater, 3) tumor size greater than 5 cm, and 4) existence of distant metastasis. A PI of $\geq 2$ indicates poor prognoses [19]. The neutrophil-to-lymphocyte ratio (NLR) is among the simple tools used for monitoring patient’s condition and evaluating treatment efficacy. NLR is calculated using the results of standardized blood tests; i.e., determined by dividing the neutrophil count by the lymphocyte count [21]. A high NLR indicates deterioration in the patient’s condition and/or the aggressiveness of the disease those resulted in poor response to the treatment and unfavorable prognoses [21].

In the present study, we reviewed our initial experiences with TKI treatment in ATC patients by two VEGF-inhibitory multi-kinase inhibitors; i.e. sorafenib and lenvatinib, with the aim of revealing the efficacy and safety of the same in clinical practice. We additionally investigated the possible indicators to prospect the efficacy of the treatment.

Patients and Methods

Data of ATC patients who received TKI therapy were retrospectively reviewed. A total of 20 patients were diagnosed with ATC at our institute from 2014 to 2019. Seven patients had no indication for anticancer treatment due to extreme disease progression and were referred for palliative care. Thirteen patients were treated with TKIs, after providing informed consent. Data on the patients’ clinical characteristics and treatment course were obtained from their records, including PI and NLR. We measured the NLR at shortly before induction of treatment, the lowest during treatment and the end of treatment. The survival period was defined as the period from the diagnosis of ATC to death of any cause. The effect on the tumor was evaluated using the RECIST (ver 1.1) criteria [22] while the adverse events (AE) was evaluated using the CTCAE (ver 4.0) criteria [23]. The institutional review board of our institute approved the present study (#4380).

Statistics

Statistical analysis was performed using EZR [24]. Kaplan-Meier curves were created, and differences in the overall survival (OS) were examined by a log-rank test, with $p < 0.05$ denoting statistical significance.

Results

Table 1 demonstrates the demography of the 13 ATC patients treated with TKIs. The patients comprised four men and nine women, with a median age of 74 (40 to 82) years. Seven patients had resectable ATC, two had ATC recurrence after initial ATC treatment, and four showed ATC recurrence following initial treatment for differentiated thyroid cancer (DTC). Sorafenib and lenvatinib were administered in three and 10 patients, respectively. In two patients, sorafenib was provided as part of a clinical trial. These cases have already reported results in the trial [6]. Only a single regimen was provided to all patients, and no salvage therapy with other TKIs was administered.

The patients’ overall treatment status is shown in Fig. 1. The interval from ATC diagnosis to TKI therapy initiation varied from 0.2 to 16.7 (median 0.5) months. In five patients, treatment for ATC was initiated by methods other than TKI therapy, such as surgery, radiation or chemotherapy. The duration of TKI treatment ranged from 0.4 to 9.2 (median 1.9) months. The survival period following TKI treatment was zero to 5.3 (median 0.3) months.

Maximal response was observed, with none of the patients showing complete response (CR), three showing partial response (PR), five showing stable disease (SD), and four showing progressive disease (PD). One patient (case 12) operated on for a rapidly growing lung tumor after radioisotope therapy for multiple lung metastases from DTC. The resected lung tumor was revealed pathologically as ATC. There were still multiple metastases remained in the lung but had no evaluable ATC lesions. The overall RR was 25.0% (3/12), and the clinical benefit rate (CBR) was 66.7% (8/12). Adverse events were found in all the patients and were of a grade greater than 3 in 12 patients (92.3%). In six cases (46.1%), TKI treat-
Table 1  Thirteen patients with anaplastic thyroid cancer treated with tyrosine kinase inhibitors

| # | Age (y) | Sex | Indication | T N M Stage | PI | Initial NLR | Treatment before TKI use | TKI | Maximal response | Treatment after TKI use | Cause of death | OS (months) |
|---|--------|-----|------------|-------------|----|------------|--------------------------|-----|----------------|--------------------------|----------------|-------------|
| 1 | 82/M   |     | Rec. ATC   | 0 1         | IVA| 3.6        | Surgery (R0), EBRT, CT   | Sorafenib | PD            | Surgery (lung)           | Accident       | 17.4        |
| 2 | 79/F   |     | Primary    | 3b 1b 0     | IVB| 2.1        | None                     | Sorafenib | SD            | None                     | Suffocation    | 3.2         |
| 3 | 79/F   |     | Rec. DTC   | X X 1       | IVC| 14.3       | None                     | Sorafenib | PD            | None                     | Cachexia       | 2.9         |
| 4 | 66/F   |     | Rec. ATC   | 3b 0 1      | IVC| 4.7        | CT, Surgery (R0), EBRT, CT| Lenvatinib | PR            | None                     | Cachexia       | 22.0        |
| 5 | 67/F   |     | Primary    | 3b 1b 1     | IVC| 9.0        | Surgery (R2), EBRT, CT   | Lenvatinib | PD            | None                     | Cachexia       | 11.5        |
| 6 | 77/F   |     | Primary    | 4a 1 1      | IVC| 5.3        | EBRT, CT                 | Lenvatinib | SD            | None                     | Cachexia       | 4.7         |
| 7 | 74/F   |     | Primary    | 4a 1b 0     | IVB| 3.8        | None                     | Lenvatinib | SD            | None                     | Suffocation    | 1.8         |
| 8 | 76/F   |     | Primary    | 4a 1b 0     | IVB| 3.9        | None                     | Lenvatinib | PD            | None                     | Suffocation    | 1.6         |
| 9 | 77/F   |     | Primary    | 3b 1b 0     | IVB| 3.4        | None                     | Lenvatinib | SD            | None                     | Cachexia       | 4.8         |
| 10| 69/F   |     | Rec. DTC   | X 1b 1      | IVC| 5.2        | None                     | Lenvatinib | PR            | None                     | Cachexia       | 2.4         |
| 11| 70/M   |     | Primary    | 4a 0 0      | IVB| 2.4        | EBRT                     | Lenvatinib | PR            | None                     | Bleeding       | 18.2        |
| 12| 68/M   |     | Rec. DTC   | X X 1       | IVC| 4.8        | Surgery (lung)           | Lenvatinib | X             | None                     | Bleeding       | 10.3        |
| 13| 40/M   |     | Rec. DTC   | X X 1       | IVC| 32.6       | None                     | Lenvatinib | SD            | None                     | Bleeding       | 2.0         |

1) Indication for treatment; Rec. ATC, recurrent disease after treatment of anaplastic thyroid cancer; Primary, primary tumor of anaplastic thyroid cancer; Rec. DTC, anaplastic transformation of recurrent disease after treatment of differentiated thyroid cancer, 2) classified by TNM classification 8th edition, 3) PI, prognostic index, 4) NLR, neutrophil-to-lymphocyte ratio, 5) TKI, tyrosine kinase inhibitor, 6) EBRT, external beam radiation therapy, 7) CT, chemotherapy with weekly paclitaxel, 8) PD, progressive disease, 9) SD, stable disease, 10) PR, partial remission

OS, overall survival; ATC, anaplastic thyroid cancer; DTC, differentiated thyroid cancer

died of the disease: seven of cachexia, three of suffocation, one of esophageal bleeding, and one of cerebral bleeding. One patient (case 1) died from fall accident at home following the postoperative period for the metastatic lung tumor refractory to TKI treatment. Three patients (23.1%) survived for longer than 12 months. All three of them received conventional therapy before TKI treatment initiation. In two patients, the primary tumor was surgically resected, and in all three patients external beam radiation to the neck was provided before TKI treatment initiation (Table 1).

Five deaths occurred within 30 days after the start of TKI. In all cases, tumor size, PI score, and NLR increased, indicating death from poor disease control. There were no treatment-related deaths.

The PI ranged from 1 to 4, with a median of 2. Patients with low PI scores (0 or 1) demonstrated longer survival periods than those with high PI scores (2 to 4) (17.4 vs. 3.8 months, $p = 0.37$) (Fig. 3); however, the
difference was not statistically significant. The NLR ranged from 2.1 to 32.6 (median 4.7) before TKI treatment initiation. A rapid decrease in the NLR was observed within a month from the initiation of TKI therapy in 11 patients (84.6%). The NLR remained low during successful TKI treatment in two patients (cases 12 and 13). The NLR rose again at the time of the termination of TKI treatment in all the patients investigated (Fig. 4).

**Fig. 1** Overall treatment status. C, chemotherapy; S, surgery; R, radiation therapy; PR, partial response; SD, stable disease; PD, progressive disease; one patient had no evaluable lesion.

**Fig. 2** Overall survival period of all patients treated with tyrosine kinase inhibitors.

OS, overall survival

**Fig. 3** Overall survival period of patients stratified by prognostic index.

OS, overall survival; PI, prognostic index.

**Fig. 4** Change in the neutrophil-to-lymphocyte ratio (NLR) before, during and at the termination of treatment with tyrosine kinase inhibitors. A case (#13) with an extraordinarily high NLR (32.6, 21.9, 29.6) was omitted from the plot.

NLR, neutrophil-to-lymphocyte ratio

**Discussions**

Successful treatment with multidisciplinary treatment involving surgery, radiation, and chemotherapy [8, 25] could be achieved only in select cases without distant metastasis [26, 27]. Surgery and radiation may control local disease and prevent suffocation temporarily. Still, a majority of patients die of locally recurrent and/or
TKI for anaplastic thyroid cancer

1. Smallridge RC, Ain KB, Asa SL, Bible KC, Brierley JD, et al. (2012) American Thyroid Association Anaplastic Thyroid Cancer Guidelines Taskforce. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 22: 1104–1139.
2. Haymart MR, Banerjee M, Yin H, Worden F, Griggs JJ (2013) Marginal treatment benefit in anaplastic thyroid cancer. Asian J Surg 36: 1247–1254.
3. Sugitani I, Miyauchi A, Sugino K, Okamoto T, Yoshida A, et al. (2012) Prognostic factors and treatment outcomes for anaplastic thyroid carcinoma: ATC Research Consortium of Japan cohort study of 677 patients. World J Surg 36: 1247–1254.
4. Ito Y, Higashiyama T, Hirokawa M, Fukushima M, Inoue H, et al. (2009) Investigation of the Validity of UICC Stage Grouping of Anaplastic Carcinoma of the Thyroid. Asian J Surg 32: 47–50.
5. Higashiyama T, Ito Y, Hirokawa M, Fukushima M, Uruno
10. Takahashi S, Kiyota N, Yamazaki T, Chayahara N, Nakano K, et al. (2019) A phase II study of the safety and efficacy of lenvatinib in patients with advanced thyroid cancer. *Future Oncol* 15: 717–726.
11. Subbiah V, Kreitman RJ, Wainberg ZA, Cho JY, Schellens JHM, et al. (2018) Dabrafenib and trametinib treatment in patients with locally advanced or metastatic BRAF V600-mutant anaplastic thyroid carcinoma. *J Clin Oncol* 36: 7–13.
12. Wang JR, Zaferro ME, Dadu R, Ferrarotto R, Busaidy NL, et al. (2019) Complete surgical resection following neoadjuvant dabrafenib plus trametinib in BRAFV600E-mutated anaplastic thyroid carcinoma. *Thyroid* 29: 1036–1043.
13. Iyer PC, Dadu R, Ferrarotto R, Busaidy NL, Habra MA, et al. (2018) Real-world experience with targeted therapy for the treatment of anaplastic thyroid carcinoma. *Thyroid* 28: 79–87.
14. NCCN clinical practice guidelines in oncology, Thyroid carcinoma version 2. (2015) https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf.
15. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, et al. (2014) Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet* 384: 319–328.
16. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, et al. (2015) Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med* 372: 621–630.
17. Kiyota N, Schlumberger M, Muro K, Ando Y, Takahashi S, et al. (2015) Subgroup analysis of Japanese patients in a phase 3 study of lenvatinib in radioiodine-refractory differentiated thyroid cancer. *Cancer Sci* 106: 1714–1721.
18. Iwasaki H, Yamazaki H, Takasaki H, Suganuma N, Nakayama H, et al. (2018) Lenvatinib as a novel treatment for anaplastic thyroid cancer: a retrospective study. *Oncol letters* 16: 7271–7277.
19. Sugitani I, Kasai N, Fujimoto Y, Yanagisawa A (2001) Prognostic factors and therapeutic strategy for anaplastic carcinoma of the thyroid. *World J Surg* 25: 617–622.
20. Orita Y, Sugitani I, Amemiya T, Fujimoto Y (2011) Prospective application of our novel prognostic index in the treatment of anaplastic thyroid carcinoma. *Surgery* 150: 1212–1219.
21. Templeton AJ, McNamara MG, Seruga B, Vera-Badillo FE, Aneja P, et al. (2014) Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst* 106: dju124.
22. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, et al. (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). http://www.jcog.jp/doctor/tool/RECISTv11J_20100810.pdf 2019.Dec 17 access (In Japanese).
23. National Cancer Institute (2010) CTCAE v 4.03. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50 2019.Dec 17 access.
24. Kanda Y (2013) Investigation of the freely available easy-to-use software ‘EZR’ for medical statistics. *Bone Marrow Transplant* 48: 452–458.
25. Smallridge RC (2012) Approach to the patient with anaplastic thyroid carcinoma. *J Clin Endocrinol Metab* 97: 2566–2572.
26. Kebebew E, Greenspan FS, Clark OH, Woebker KA, McMillan A (2005) Anaplastic thyroid carcinoma treatment outcome and prognostic factors. *Cancer* 103: 1330–1335.
27. Foote RL, Molina JR, Kasperbauer JL, Lloyd RV, McIver B, et al. (2011) Enhanced survival in locoregionally confined anaplastic thyroid carcinoma: a single-institution experience using aggressive multimodal therapy. *Thyroid* 21: 25–30.
28. Kitamura Y, Shimizu K, Nagahama M, Sugino K, Ozaki O, et al. (1999) Immediate causes of death in thyroid carcinoma: clinicopathological analysis of 161 fatal cases. *J Clin Endocrinol Metab* 84: 4043–4049.
29. Onoda N, Sugitani I, Ito KI, Suzuki A, Higashiya T, et al. (2020) Evaluation of the 8th Edition TNM Classification for Anaplastic Thyroid Carcinoma. *Cancers (Basel)* 12: 552.