Anaplastic Thyroid Carcinoma Treated with Lenvatinib

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Summary: Objective: We report a case of anaplastic thyroid carcinoma (ATC) with local recurrence and distant metastasis that responded very well to treatment with lenvatinib, a new molecular-targeted anticancer drug. Case Report: A 91-year-old Japanese woman presented with a 5-month history of a painless mass in her left anterior neck. She had a past history of total thyroidectomy and neck dissection for papillary carcinoma of the thyroid. Here she underwent neck dissection, and the histopathological diagnosis was lymph node metastasis of papillary carcinoma with anaplastic transformation. Five months later, a cervical lymph node swelled up again. Computed tomography demonstrated an enhanced mass in the neck and multiple nodules in both lungs. Recurrent ATC with multiple lung metastases was diagnosed, and molecular-targeted therapy with lenvatinib was initiated. The neck tumor reduced in 1 week, and the pulmonary nodules became completely hollow within 1 month. However, we had to discontinue lenvatinib because of severe side effects including high blood pressure, hypocalcemia, and hypoalbuminemia. Soon after discontinuation, the side effects subsided, but the tumor rapidly regrew. The patient died of lymphangiosis carcinomatosa 6 days after discontinuation. Conclusion: Although recent advances in molecular-targeted therapy have provided powerful cancer therapy tools, the negative side of this therapy must be addressed.

Key words anaplastic thyroid carcinoma, lenvatinib, tyrosine kinase inhibitor, molecular-targeted therapy, clinical effect

INTRODUCTION

Anaplastic thyroid carcinoma (ATC), which accounts for 1%-2% of all malignant tumors of the thyroid, is known to be highly resistant to any therapy and has a 1-year survival rate of 5%-20% [1-3]. ATC patients are limited in number, and most die within 6 months after diagnosis, making it difficult to establish a standard treatment protocol. Multimodal therapy including surgery, radiotherapy and chemotherapy has been introduced, but survival times remain poor [4-6].

The use of molecular-targeted drugs as cancer therapy has been rapidly increasing over the past decade. Lenvatinib, a new molecular-targeted anticancer drug, is a multi-targeted receptor tyrosine kinase inhibitor that inhibits the activities of vascular endothelial growth factor receptors, fibroblast growth factor receptors, platelet-derived growth factor receptors, KIT, and RET [7, 8]. Lenvatinib exerts its anticancer activity via the suppression of tumor angiogenesis, and it is generally indicated for unresectable radioiodine-refractory differentiated thyroid cancers [9]. However, the evidence of the clinical effect of this drug on ATC is very limited.

We herein report a case of ATC with local recur-
rence and distant metastasis that responded extremely well to the administration of lenvatinib, although the treatment was not without a downside.

CASE REPORT

A 91-year-old Japanese woman was referred to our department with a 5-month history of a painless mass that was gradually increasing in size in the left anterior neck. She had undergone a total thyroidectomy and D1 neck dissection for papillary carcinoma of the thyroid 16 years earlier. The mass was elastic, hard and mobile, and measured 20 mm in diameter at the time of consultation. Skin flare was not seen. On endoscopic examination the nasal cavity, pharynx and larynx were normal with intact vocal cord movement. Computed tomography (CT) demonstrated a solid mass with peripheral contrast enhancement adjoining the left side of the thyroid cartilage (Fig. 1a). Adipose tissues around the mass showed a misty contrast effect. Positron emission tomography revealed a significant FDG uptake by the mass (SUV$_{\text{max}}$=28.9; Fig. 1b) without FDG uptake in any other sites. A fine needle aspiration biopsy showed many undifferentiated atypical cells, and the lesion was diagnosed as a class V undifferentiated carcinoma metastasizing to the lymph node. The histological type was not determined.

Under the clinical diagnosis of occult primary tumor of the neck, we performed a left neck dissection at the levels II-V and left tonsillectomy with the patient under general anesthesia. The histopathological examination of the surgical specimens revealed metastatic lymph nodes with the anaplastic transformation of papillary carcinoma (Fig. 2). Extracapsular extension of the carcinoma was observed in the level IIA lymph node. The tonsil was free of carcinoma. Because the patient was very elderly, we conducted close follow-up observation and did not perform postoperative treatment such as adjuvant chemoradiotherapy. The postoperative course was uneventful, and the patient was discharged 10 days after the surgery.

Five months later, a left cervical lymph node swelled up again. CT demonstrated a 35-mm enhanced tumor in the left level IB and multiple nodules in both lungs (Fig. 3). The patient was then diagnosed with recurrent ATC with multiple lung metastases, and we initiated an oral administration of lenvatinib (24 mg/day). The tumor in the neck rapidly reduced within 1 week, and CT at 1 month after the initiation of lenvatinib showed that the pulmonary nodules were completely hollow (Fig. 4). The therapeutic effect was judged as a ‘good partial response’ according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

She had been taking antihypertensive drugs (angiotensin receptor blocker and β-blocker) and continued

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**Fig. 1.** Imaging findings at the patient’s first visit.
(a) CT demonstrated a 20-mm solid mass with peripheral contrast enhancement adjoining the left side of the thyroid cartilage.
(b) PET revealed a significant FDG uptake by this mass (SUV$_{\text{max}}$=28.9).
taking them after the initiation of lenvatinib. However, several severe side effects emerged: high blood pressure as an immediate reaction, hypocalcemia with tetany at 2 weeks, and severe hypoalbuminemia caused by albuminuria and diarrhea at 3 weeks after the initiation of lenvatinib. We had no choice but to taper the dose of lenvatinib. The dose was reduced to 20mg/day, but her condition remained critical. We eventually discontinued the lenvatinib by the 40th day of administration. The level of proteinuria examined by a urine test strip was >300 mg/dl at discontinuation of lenvatinib. Although the side effects subsided soon after the discontinuation, the cervical lymph nodes and pulmonary nodules rapidly increased in size again. We visited the patient in the ward at least twice a day, performed blood tests 2-3 times a week, and continuously monitored her condition by electrocardiograph and pulse oximeter. Although we took various possible measures against hypocalcemia, tetany, hypoalbuminemia, albuminuria and diarrhea, she did not recover. Infiltrative shadows spread in both lungs, and the patient died of lymphangiosis carcinomatosa 6 days after the discontinuation of lenvatinib. She survived for 45 days after the initiation of lenvatinib.

**DISCUSSION**

Anaplastic transformation of differentiated thyroid carcinoma is sometimes seen in the primary lesions of elderly people, but its occurrence in metastatic lesions as in the present case is relatively rare. Sugitani et al. [5] conducted a multicenter cohort study to investigate prognostic factors and treatment outcomes of ATC. Of the study population of 677 patients with ATC, 95 patients (14.0%) showed anaplastic transformation at the neck lymph nodes. Several negative prognostic factors were identified by this case-control study [5]: (i) acute exacerbation within 1
Several authors have shown that survival period in patients with resectable ATC [5, 12-14]. Several authors have shown that ATC cases. Although (chemo)radiation is generally ineffective against ATC [2, 4, 5], it has been documented that postoperative hyperfractionated radiotherapy improved local control [12, 15].

The combination of taxane and cisplatin is recommended as chemotherapy for ATC, but it has not led to a significant extension of survival time [16]. In recent years, molecular biological studies have revealed that the mutation of the genes BRAF and N-RAS is associated with anaplastic transformation (17, 18), and conventional cancer chemotherapy has been shifting to molecular-targeted therapy.

As a multi-targeted receptor tyrosine kinase inhibitor, lenvatinib has been shown to have a strong antitumor effect on thyroid cancers. According to the 2014 U.S. National Comprehensive Cancer Network guidelines, kinase inhibitor therapy may be indicated for differentiated thyroid carcinomas that are symptomatic and/or progressive and unamenable to radiiodine therapy [19]. This criterion was supported by the results of a randomized, double-blind, multinational, phase III SELECT study [9], in which patients with radioidine-refractory differentiated thyroid cancers received 24-mg once-daily oral lenvatinib (261 patients) or placebo (131 patients) in 28-day cycles. The lenvatinib treatment significantly improved the median progression-free survival time and overall response rate. However, this trial also reported a high incidence of grade 3 treatment-related side effects including hypertension (42%), weight loss (10%), proteinuria (10%), fatigue (9%), diarrhea (8%), stomatitis (4%), hand-foot syndrome (3%), and nausea (2%) (9).

The effects of lenvatinib on ATC have been documented in vitro and in an experimental animal model [8], but, to the best of our knowledge, there is no previous paper showing the clinical effect of this drug on ATC. Savvides et al. conducted a phase II trial of another tyrosine kinase inhibitor, sorafenib, in patients with advanced ATC, and they reported that 2 of 20 patients (10%) showed a partial response [20].

The present patient developed local recurrence and multiple lung metastases only 5 months after the radical resection, and she received molecular-targeted therapy with lenvatinib. We observed some conspicuous findings in the patient’s clinical course. First, a good partial response was obtained by using this molecular-targeted therapy, demonstrating high efficacy of lenvatinib for the suppression of ATC. Second, together with the strong antitumor effect, lenvatinib also caused several uncontrollable side effects, i.e., high blood pressure, hypocalcemia with tetany, albuminuria, diarrhea, and severe hypoalbuminemia. The lenvatinib had to be discontinued within 6 weeks of its initiation. Particularly in elderly patients, the appropriate dosage of lenvatinib and effective treatment to relieve harmful side effects should be reconsidered. It might have been better to start with a reduced dose of lenvatinib and to have begun palliative care earlier. Third, the lesions in the patient’s neck and lung rapidly regrew immediately after the cessation of lenvatinib, and the patient died only 6 days later. The mechanisms underlying such a drastic rebound phenomenon should be investigated in order to find alternative measures to use upon the withdrawal of lenvatinib. At the present time, the only measures to cope with rapid tumor progression after the discontinuation of lenvatinib would be case-by-case palliative care.

It is questionable whether the administration of lenvatinib extended the patient’s survival time and/or relieved her physical burden. However, the use of lenvatinib was the patient’s and her family’s own choice after careful informed consent, and we believe that she felt mental relief during the short period of the remission of disease.

CONCLUSIONS

We reported a case of an ATC patient with local recurrence and lung metastasis who was treated with
lenvatinib. This molecular-targeted drug exhibited a strong antitumor effect on the conventionally incurable patient, but it also caused uncontrollable side effects. In addition, the withdrawal of lenvatinib led to a marked regrowth of the tumor. Although recent advances in molecular-targeted therapy have provided us with powerful tools in cancer therapy, clinicians need to simultaneously address the negative side of this therapy.

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