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Case Report

Effective Lenvatinib Treatment Complicated with Secondary Tracheocutaneous Fistula in Patients with Advanced Anaplastic Thyroid Carcinoma

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Abstract: Anaplastic thyroid carcinoma (ATC) is a fatal disease with a poor prognosis. Lenvatinib is an oral multi-targeted tyrosine kinase inhibitor (TKI) which is approved in Japan for the treatment of ATC. Data of treatment response and adverse effects of lenvatinib in ATC patients is still relatively scarce, especially in non-Japanese patient populations. Here we report dramatic treatment effects of lenvatinib in two patients with stage IVc ATC, who later developed significant morbidities including tracheal perforation and fistula formation. Our cases demonstrate the efficacy and provide cautionary information for treatment of ATC. In treating advanced ATC patients with lenvatinib, close monitoring is highly recommended.

Keywords: lenvatinib; anaplastic thyroid carcinoma (ATC); tracheocutaneous fistula; tumor-cutaneous fistula; carotid blowout syndrome

1. Introduction

Anaplastic thyroid carcinoma (ATC) accounts for only 1–2% of thyroid cancer but contributes to more than 50% of thyroid cancer-related mortalities [1]. Patients with ATC have a poor prognosis, with a median survival of 5–6 months [2,3]. Treatment outcome of ATC is often unsatisfactory by conventional chemotherapeutics or even combined multi-modality treatments [1,4].

Lenvatinib, an oral multi-targeted tyrosine kinase inhibitor (TKI), was approved as treatment of locally advanced or recurrent, radioactive iodine (RAI) refractory differentiated thyroid cancer (DTC) [2]. It has been approved as a treatment for ATC in Japan. Recently, a retrospective study composed of 23 Japanese patients with ATC treated with lenvatinib showed an incidence of 39.1% grade 3 or higher treatment-related adverse events [5]. Hypertension was the most common adverse effect (AE), while headache, gastrointestinal discomfort, rare complications such as tumor fistula, and carotid blowout syndrome were also described [5]. Similar clinical data is relatively scarce, especially in non-Japanese patients with ATC. Here we report two cases with stage IVc ATC who received lenvatinib treatment. Both patients initially had bulky tumor with tracheal compression and distant metastasis. Although lenvatinib led to massive tumor necrosis and shrinkage, it then unfortunately resulted in significant morbidities, including tracheal perforation and fistula formation.

2. Case Presentation

The patients had fully consented to reporting and publishing of this manuscript.

2.1. Case 1

A 58-year-old male patient who weighed 50 kg came to our hospital due to progressive hoarseness, swallowing difficulty, and an enlarging neck mass. Following workup yielded a diagnosis of anaplastic thyroid carcinoma with tracheal compression, lung and bone metastasis, and a clinical staging of cT3N1M1, stage IVc. Due to encasement of the trachea, esophagus and carotid artery, surgery was deemed high risk and was not done. He then received lenvatinib 20 mg daily. One month later, he experienced a sudden onset of breathing difficulty with rapid desaturation. Emergent endo-tracheal intubation was performed and lenvatinib was withheld. A deep skin defect over the neck was noticed. Computed tomography (CT) studies favored abscess formation with mediastinitis and presence of pneumomediastinum, as well as tracheocutaneous fistula formation (Figure 1). Bronchoscope examination revealed perforation of right lateral-posterior wall of trachea, two cm below vocal cords and a fistula formation between trachea and skin. Emergent video-assisted thoracoscopic (VATS) decortication was done with chest tube insertion. Ten days later, leakage of air from the skin wound was still present even the patient was still under tracheal tube intubation. Bronchoscope exam revealed a perforation about 1.7 cm in length with persistent tracheocutaneous fistula (Figure 2). Surgical repair by tracheoplasty was performed with tracheostomy to support respiration, leaving an open wound for pus drainage (Figure 3). The patient was stabilized and the breathing status as well as oxygenation was relatively normal. After 2 months of cessation of lenvatinib, the patient was re-started on lenvatinib at a reduced dosage of 10 mg every other day. Although his condition stabilized, the patient ultimately expired due to respiratory complications two months later.

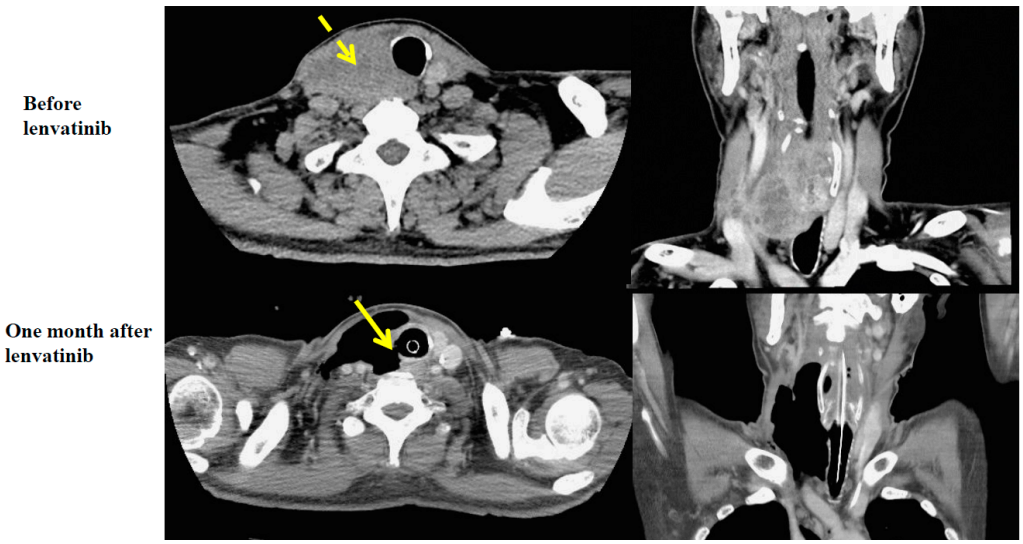


Figure 1. Marked necrosis of previously noted right thyroid tumor and large cavity with air and fluid content 1 month after lenvatinib. The dotted arrow of the upper panel: a bulky tumor mass. The yellow arrow of the lower panel: marked necrosis of previous tumor and tumor-tracheal fistula.

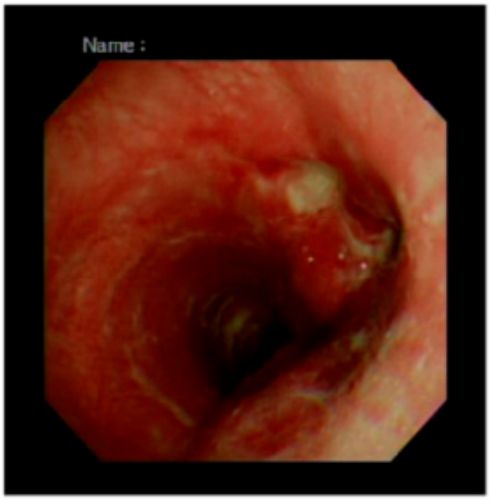


Figure 2. Bronchoscope exam demonstrated perforation of right lateral-posterior wall of trachea, about 1.7 cm in length, 2 cm below vocal cords and a tumor-tracheo-cutaneous fistula formation.

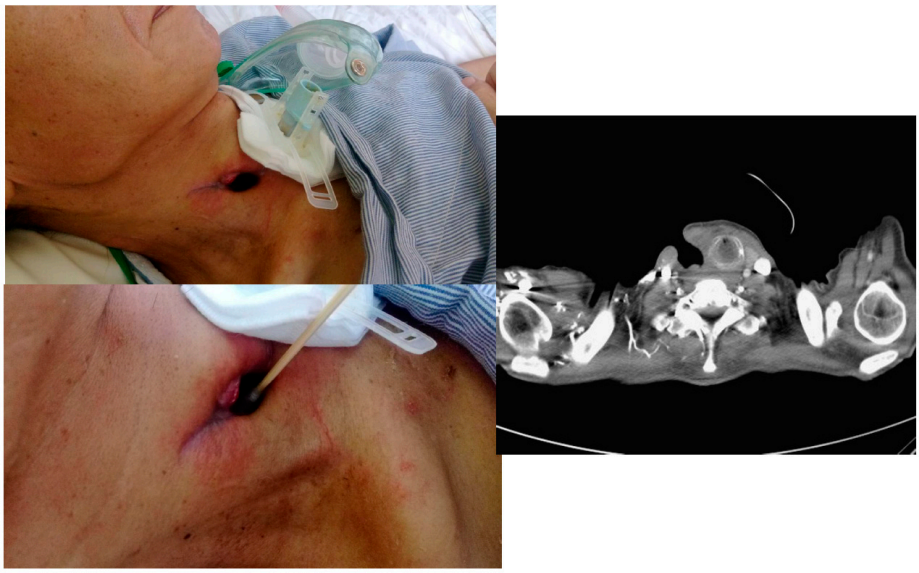
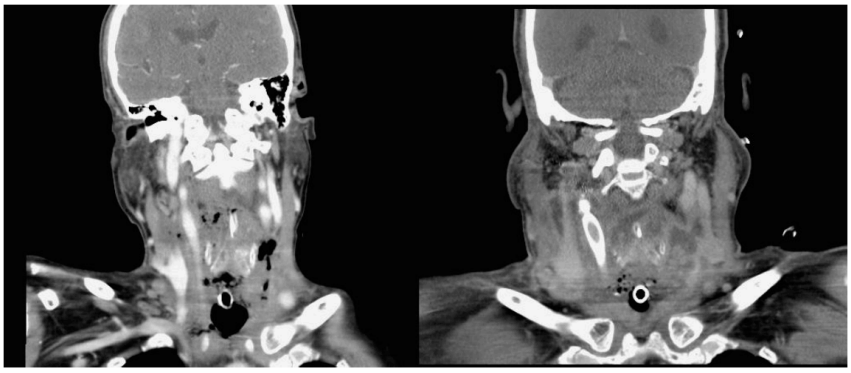


Figure 3. Clinical presentation and CT (computed tomography) scan image after tracheoplasty of case 1. CT scan also demonstrated a residual tumor-cutaneous fistula.

2.2. Case 2

A 67-year-old male patient was diagnosed with advanced ATC, complicated with neck, mediastinum and lung metastases, and initial stage IVc at a local hospital, where he received a wide excision of thyroid tumor and tracheostomy implantation. One month after the surgery, he came to our hospital and was started on lenvatinib 10 mg daily. On the 30th day of lenvatinib, massive bleeding came out from the tracheostomy and mouth. Emergent carotid angiography disclosed irregular vascular stump of the right superior thyroid artery and the necrotic tumor tissue encasing the right carotid artery (Figure 4). Five fiber coils and a 10 × 100 mm Viabahn stent-graft were deployed to right external, internal, and common carotid arteries. A reduced dose of lenvatinib (10 mg every other day) was added for a second time 2 weeks later.



(A) (B)

Figure 4. (**A**) Computed tomography of case 2. The thyroid cancer encased the right common carotid artery (CCA) and external carotid artery (ECA). (**B**) Stent graft insertion and coil embolization over right carotid artery.

However, fourteen days after the resume of lenvatinib, milk-like discharge leaked out from tracheostomy and para-tracheostomy wound. The wound around the tracheostomy gradually enlarged in the next 2 weeks with extravasation of blood-tinged discharge. Further image study revealed a tracheocutaneous fistula (Figure 5). The trachea was fragile under endoscopic examination and was deemed inoperable by our chest surgeon expert. The patient developed clinical respiratory distress with intermittent desaturation despite ventilator support. The patient died of respiratory failure 3.5 months after the first day of lenvatinib.

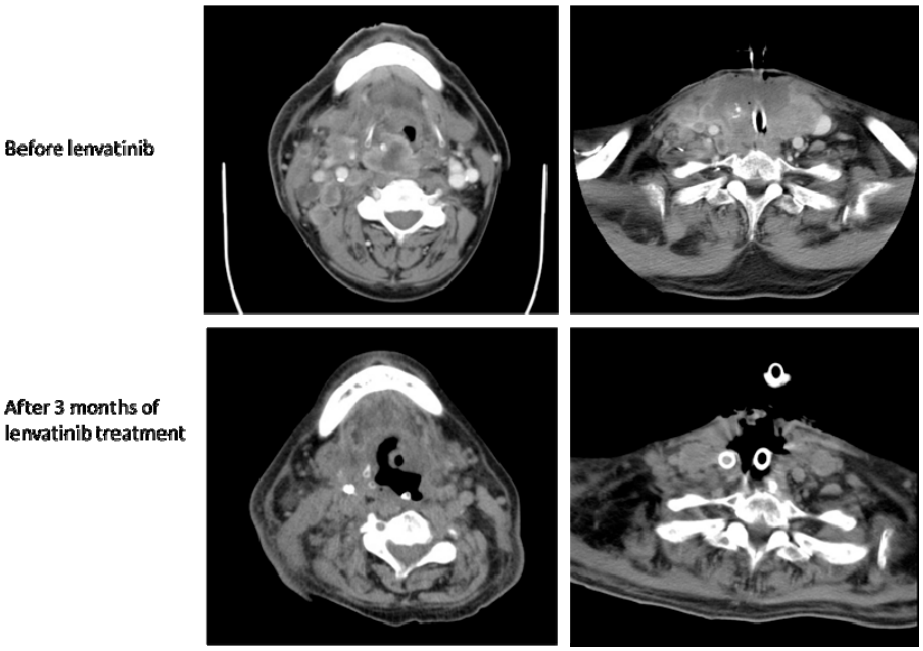


Figure 5. Necrotic tumor with large open wound around tracheostomy with tracheocutaneous fistula. Upper panel: before lenvatinib treatment. Lower panel: 3 months after lenvatinib treatment.

3. Discussion

ATC is a lethal disease with poor outcome and is generally refractory to standard chemotherapy. Lenvatinib is a multi-tyrosine kinase inhibitor with targets including VEGFR1-3, FGFR1-4, PDGFR-alpha, RET and KIT proto-oncogenes [6]. The efficacy of lenvatinib in refractory well-differentiated thyroid cancer was demonstrated in a landmark trial in 2015 [7]. In that trial, up to 75.9% patients reported grade 3 or higher AEs, and 14% patients discontinued the drug accordingly. The most common side effects

include hypertension, diarrhea, and a decrease of appetite, nausea, and proteinuria. Six deaths were considered treatment related, including one case of pulmonary embolism and another of hemorrhagic stroke. No tracheoesophageal fistula or carotid blow out events were demonstrated in this trial.

Lenvatinib was relatively recently approved in Japan alone as a treatment for ATC. Real world experience of lenvatinib in ATC is still relatively lacking, especially reports regarding safety and adverse events in clinical use. A study of Japanese demonstrated 23 patients with advanced stage (IVb and IVc) ATC who received lenvatinib (with a dosage ranging from 10 mg to 24 mg daily) [5]. The authors reported an overall response rate of 17.4% and a disease control rate (DCR) of 43.5%. The median overall survival time was 166 days. However, there was a striking 39.1% incidence of grade 3 or more AEs leading to termination of treatment. Six out of the 23 patients had tumor-cutaneous fistulas, including one with carotid blow out. The result suggested that lenvatinib was accompanied by significant morbidities in ATC patients [5]. Relevant to our current report, both of the patients developed tracheal fistula formation and ultimately died of aspiration pneumonia.

It is likely that lenvatinib not only causes tumor necrosis but also surrounding tissue damage. Experience derived from our patients would suggest that in advanced ATC patients with bulky tumor size, tumor encasement of major vessels of neck or with proximity to trachea, it might be prudent to reduce the dosage of lenvatinib. Regardless of the dose used, close monitoring of clinical symptoms, signs and regular imaging follow up will be helpful. To minimize risks of rapid tumor shrinkage leading to AEs, we suggest a reduced dose or frequency of lenvatinib such as 10 milligrams every other day be used in high-risk patients. Patients who have started lenvatinib presenting with shortness of breath, choking episodes, food regurgitation from airway, or an increase of oxygen demand should promptly be evaluated with bronchoscope examination and imaging studies to early detect possible tracheal fistula. Surgical intervention including tracheal defect repair, tracheostomy, and stenting might be indicated once tracheal defect is confirmed. In the occurrence of the aforementioned AEs, discontinuation or dose adjustment of lenvatinib is required. Lenvatinib inhibits VEGF and consequently leads to cessation of pathogenic angiogenesis [8]. The role of prophylactic tracheostomy to prevent tracheal fistula is unclear in this situation due to the possibility of poor wound healing induced by lenvatinib [9].

4. Conclusions

In conclusion, we present two patients with stage IVc ATC who responded dramatically to lenvatinib with significant tumor shrinkage. However, overly rapid necrosis of the tumors led to life threatening AEs. Our case presentation serves as an important reference to treatment consideration of advanced ATC. Physicians should be aware of this potentially high-risk treatment and closely monitor the clinical status of patients treated with lenvatinib. Any warning signs should prompt further workup to prevent a possible fatal outcome.

Author Contributions: C.-Y.L. conceived and designed the study and contributed to the treatment planning. W.-C.W. acquired the laboratory and clinical data and wrote the manuscript. J.-Y.C. a surgeon specialized in thyroid cancer and consultant. C.-Y.L., J.-Y.C. and J.-I.L. made critical revisions. All authors participated in the multidisciplinary conference and approved the final version of the manuscript.

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Conflicts of Interest: The authors have no potential conflicts of interest to disclose.

References

1. Saini, S.; Tulla, K.; Maker, A.V.; Burman, K.D.; Prabhakar, B.S. Therapeutic advances in anaplastic thyroid cancer: A current perspective. *Mol. Cancer* **2018**, *17*, 154. [CrossRef]
2. Sugitani, I.; Miyauchi, A.; Sugino, K.; Okamoto, T.; Yoshida, A.; Suzuki, S. Prognostic factors and treatment outcomes for anaplastic thyroid carcinoma: ATC Research Consortium of Japan cohort study of 677 patients. *World J. Surg.* **2012**, *36*, 1247–1254. [CrossRef]

3. Keutgen, X.M.; Sadowski, S.M.; Kebebew, E. Management of anaplastic thyroid cancer. *Gland Surg.* **2015**, *4*, 44–51.
4. Glaser, S.M.; Mandish, S.F.; Gill, B.S.; Balasubramani, G.K.; Clump, D.A.; Beriwal, S. Anaplastic thyroid cancer: Prognostic factors, patterns of care, and overall survival. *Head Neck* **2016**, *38*, E2083–E2090. [CrossRef]
5. Iwasaki, H.; Yamazaki, H.; Takasaki, H.; Suganuma, N.; Nakayama, H.; Toda, S.; Masudo, K. Lenvatinib as a novel treatment for anaplastic thyroid cancer: A retrospective study. *Oncol. Lett.* **2018**, *16*, 7271–7277. [CrossRef]
6. Tahara, M.; Kiyota, N.; Yamazaki, T.; Chayahara, N.; Nakano, K.; Inagaki, L.; Toda, K.; Enokida, T.; Minami, H.; Imamura, Y.; et al. Lenvatinib for Anaplastic Thyroid Cancer. *Front Oncol.* **2017**, *7*, 25. [CrossRef]
7. Schlumberger, M.; Tahara, M.; Wirth, L.J.; Robinson, B.; Brose, M.S.; Elisei, R.; Habra, M.A.; Newbold, K.; Shah, M.H.; Hoff, A.O.; et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N. Engl. J. Med.* **2015**, *372*, 621–630. [CrossRef]
8. Okamoto, K.; Ikemori-Kawada, M.; Jestel, A.; von König, K.; Funahashi, Y.; Matsushima, T.; Tsuruoka, A.; Inoue, A.; Matsui, J. Distinct binding mode of multikinase inhibitor lenvatinib revealed by biochemical characterization. *ACS Med. Chem. Lett.* **2015**, *6*, 89–94. [CrossRef]
9. Shah, D.R.; Dholakia, S.; Shah, R.R. Effect of tyrosine kinase inhibitors on wound healing and tissue repair: Implications for surgery in cancer patients. *Drug Saf.* **2014**, *37*, 135–149. [CrossRef]