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Surgical treatment of locally advanced papillary thyroid carcinoma after response to lenvatinib: A case report

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ABSTRACT

INTRODUCTION: Differentiated thyroid carcinomas (DTC) have good prognoses after complete resection. Nevertheless, when DTC is associated with an aerodigestive invasion, curative surgery is difficult to perform. However, there is no established neoadjuvant therapy for advanced DTC.

PRESENTATION OF CASE: A 73-year-old man with thyroid papillary carcinoma was referred to our hospital. A computed tomography examination revealed a tumor in the upper right lobe of the thyroid, and multiple bilateral enlarged lymph nodes in the neck, involving the surrounding structures. The enlarged lymph node at the right upper neck was suspected to have invaded the right internal jugular vein, and the left paratracheal lymph node was suspected to have invaded the cervical esophagus and trachea. The tumor was considered resectable; however, surgery would have been highly invasive. Therefore, we initiated neoadjuvant therapy with lenvatinib. After administration of lenvatinib, the tumor decreased in size by 84.3% and the cervical lymph nodes by 56.0%. The patient underwent a total thyroidectomy, modified neck dissection, a resection of the muscular layer of the esophagus, and a tracheal sleeve resection and reconstruction.

DISCUSSION: The SELECT trial demonstrated that lenvatinib had high response rate with short response time, in patients with radioiodine-refractory DTC. The results suggested that lenvatinib could be effective as neoadjuvant therapy.

CONCLUSION: For an advanced DTC that requires removal through invasive surgery, preoperative lenvatinib treatment might be one of the options for a less invasive surgery.

1. Introduction

Generally, differentiated thyroid carcinomas (DTC) have good prognoses after complete resection; most patients with DTC are treated with a primary surgery. However, we sometimes encounter patients with locally advanced DTC, which has invaded surrounding structures. Direct invasion of the larynx, trachea, pharynx, esophagus, recurrent laryngeal nerve, strap muscles, and/or carotid artery occurs in 7–16% of patients with thyroid cancer [1]. The treatment strategy is difficult in such cases because it is difficult to resect completely, a locally advanced DTC without invasion of these critical structures.

Guidelines of the American Thyroid Association [2] recommend that the surgical removal of an aerodigestive invasive DTC should be performed in combination with radioactive iodine (RAI) therapy, and/or external beam radiotherapy. However, there are few institutions permitted to perform RAI therapy in Japan because of severe restrictions in the handling of RAI. Therefore, a patient in need of RAI will have to wait for an unreasonable length of time to have access to the therapy. Moreover, a neoadjuvant external beam radiation therapy can lead to fibrosis, which can make surgery even more complicated for the surgeon.

Lenvatinib is an oral, multitargeted tyrosine kinase inhibitor (TKI) of the VEGFRs 1–3, FGFRs 1–4, PDGFR α, RET, and KIT signaling networks [3,4]. Previously reported results of the SELECT trial demonstrated that lenvatinib significantly prolonged progression-free survival (PFS) in patients with RAI-refractory DTC, compared with those on placebo [5]. Based on this and several other reports [6,7] about the role of chemotherapy in DTC, unresectable locally advanced DTC that invades critical structures can become resectable after neoadjuvant chemotherapy with lenvatinib. However, there has been no report on neoadjuvant chemotherapy in advanced DTC with TKI.

We report on a locally advanced papillary thyroid carcinoma, which was difficult to resect because of invasion of the jugular vein, trachea, and esophagus, in a 73-year-old man who underwent surgery after preoperative chemotherapy with lenvatinib.

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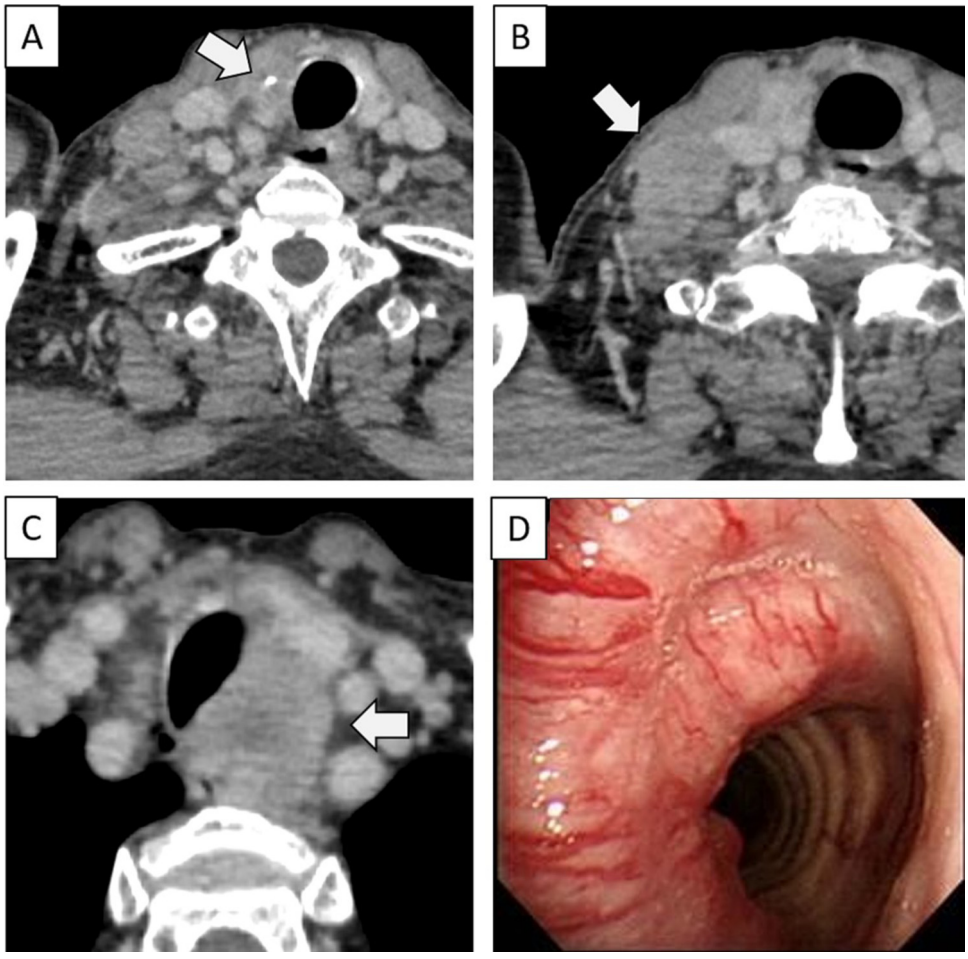

Fig. 1. A computed tomography examination revealed a mass, measuring 18 × 17 mm in the upper right lobe of thyroid (A) and swollen lymph nodes in neck: the lymph node at the right upper neck suspected invasion of right internal jugular vein (B), the left paratracheal lymph node suspected invasion of cervical esophagus and trachea (C). Bronchoscope examination revealed tumor invasion in tracheal lumen (D).

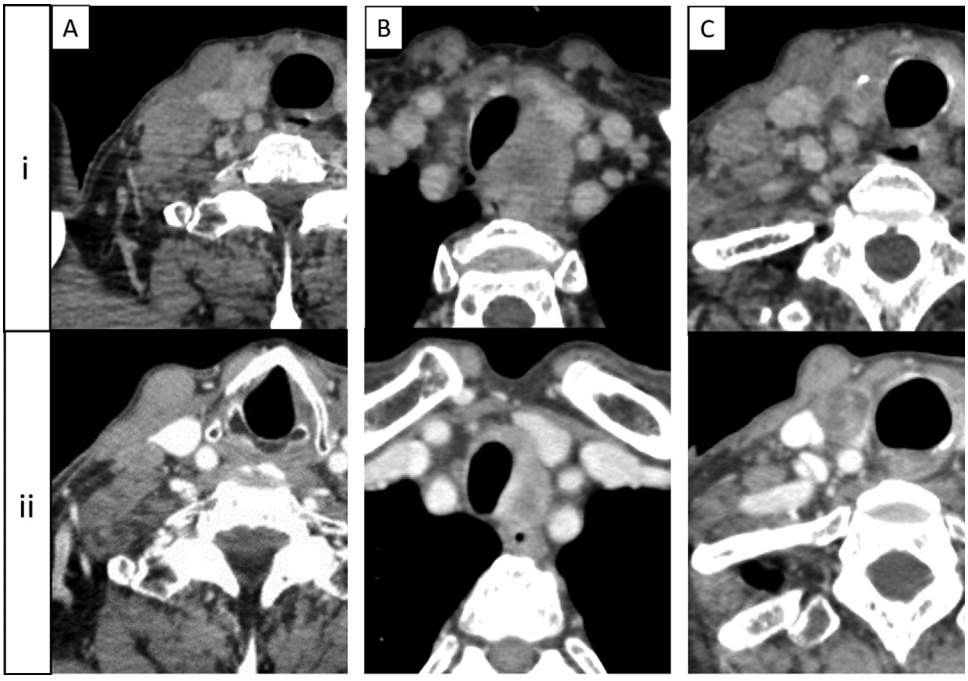

Fig. 2. A computed tomography examination showed tumor reduction: (A) lymph node at the right neck decreased in size by 84.3%, (B) left parabronchial lymph node decreased in size by 56.0%, and (C) thyroid tumor decreased in size by 5.9%. (i) before treatment, (ii) after treatment.

This manuscript has been reported in accordance with the SCARE criteria [8].

2. Case presentation

A 73-year-old man presented to a hospital with a right neck mass and hoarseness. He was diagnosed with a thyroid papillary carcinoma, and was referred to our hospital for further treatment. Upon physical examination, we found a large hard immobile mass in the right neck. Standard laboratory test results on serum and urine showed no significant findings. Thyroid function test showed low thyroid-stimulating hormone (TSH): 0.03 μU/mL (reference range: 0.74–4.12), normal free thyroxine (fT4): 1.18 ng/dL (reference range: 0.70–1.25), and high free triiodothyronine (fT3): 3.6 pg/mL (reference range: 2.5–3.5). Thyroglobulin level was elevated to 478 ng/mL (reference range ≤33.7). Tumor markers such as carcinoembryonic antigen and squamous cell carcinoma antigen were within the reference limits. Computed tomography (CT) revealed a mass, measuring 18 × 17 mm in the upper right lobe of the thyroid, and multiple bilateral lymph nodes in the neck, involving surrounding structures. The enlarged lymph node, measuring 43 × 27 mm at the right upper neck was suspected to have invaded the right internal jugular vein. The left paratracheal lymph node, measuring 30 × 25 mm was suspected to have invaded the cervical esophagus and trachea (Fig. 1A–C). These lymph nodes were not biopsied; however, they were considered lymph node metastases by CT findings. There was no apparent distant metastasis. A bronchoscopy revealed a tumor invasion in the tracheal lumen (Fig. 1D). An esophagogastroduodenoscopy revealed the absence of a tumor invasion in the inner lumen of the esophagus. However, the procedure to dissect the tumor and concurrently preserve the cervical esophagus was considered difficult, since according to the CT, the tumor and the cervical esophagus had no defined boundaries. A diagnosis of clinical thyroid papillary carcinoma (T4a N1b M0, stage IVA) was made. We judged the tumor as resectable; however, we were concerned that a resection and reconstruction of a wide stretch of the esophagus and trachea would be highly invasive. We explained the condition of the disease and our planned procedure; however, the patient refused immediate surgery owing to the high invasiveness of the procedure. On the other hand, the patient would have had to wait for nearly one year in our hospital, to have access to RAI therapy. Due to the above reasons, he began chemotherapy treatment with lenvatinib. Since the tumor was suspected to have invaded the trachea, the muscular layer of the esophagus, and the right internal jugular vein, lenvatinib administration was started at 14 mg per body weight, considering, the possibility for aerodigestive fistula and tumor bleeding. Although grade 3 proteinuria and hypertension were observed, these were controlled with antihypertensive agents, dose reduction of lenvatinib, and the withdrawal of chemotherapy. A follow-up CT examination was performed on the patient to assess the therapeutic effect of lenvatinib. After administration of lenvatinib (total dose, 966 mg for 22 weeks; including total of 4 weeks of withdrawal during the administration period), the tumor decreased in size by 84.3%, the cervical lymph nodes by 56.0% (Fig. 2A, B), and the thyroid papillary carcinoma by 5.9% (Fig. 2C). The metastatic lymph node and cervical esophagus showed well-defined boundaries. Thyroglobulin level decreased to 101 ng/mL. Bronchoscopy showed a residual tumor in the tracheal lumen; however, the tumor was reduced (Fig. 3). Based on these findings, we believed that surgery could be less invasive, and thus, the cervical esophagus could be preserved. Eventually, the patient consented to surgery, which he underwent after 17 days from the last administration of lenvatinib. The surgical procedure consisted total thyroidectomy, a modified right neck dissection, a resection of the muscular layer of the esophagus, and a tracheal sleeve resection and reconstruction. A cavity was located in the resected thyroid tumor; this might have been the result of tumor necrosis, caused by the efficacy of the lenvatinib therapy. He was discharged 14 days after the surgery without postoperative complications, or adjuvant chemotherapy. No macroscopic residual tumor was found in the surrounding tissues during the operation, but histologically, a microscopic invasion was found at the edge of the resected bronchial wall. An appointment was booked after 11 months for RAI therapy. There has been no distant metastasis for 10 months post-surgery.

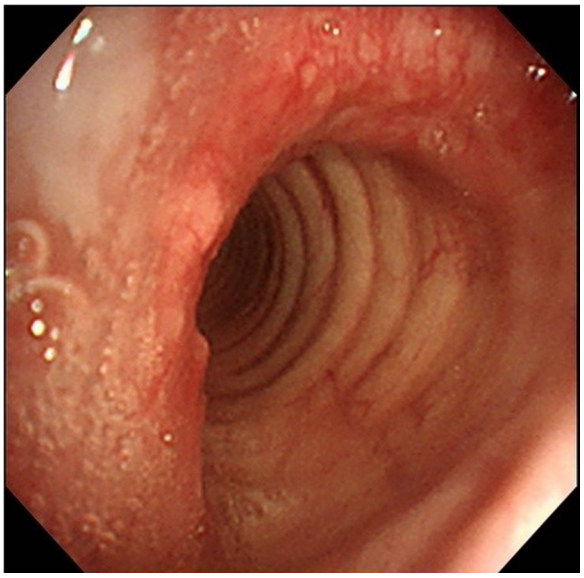

Fig. 3. After lenvatinib therapy, a bronchoscopy showed a residual tumor in the tracheal lumen, but tumor was reduced.

3. Discussion

Although there are some reports of preoperative therapy for DTC, there is no established neoadjuvant therapy for advanced DTC because it is not common to have a difficult complete resection of a DTC.

Shingu et al. reported a case of resection of locally advanced DTC after response to preoperative RAI therapy [9]. In their case, unresectable DTC became resectable due to RAI therapy; therefore, preoperative therapy for advanced DTC is considered very effective.

There have been some reports of neoadjuvant chemotherapy for DTC [6,7]. Basic et al. reported findings of patients with T3/T4 papillary thyroid carcinoma who were treated with neoadjuvant chemotherapy of vinblastine, Adriamycin, or other regimens; tumor size decreased by >50% in 44.8% of the patients. They also reported that neoadjuvant chemotherapy in patients with locally advanced follicular or Hürthle cell thyroid carcinoma reduced tumor size by >50% in 45% of those patients. Based on the results of these studies, we hypothesized that neoadjuvant chemotherapy might be effective in DTC.

Generally, targeted therapy is considered more effective and less toxic than conventional cytotoxic chemotherapy. However, no study has been conducted to assess the effect of neoadjuvant chemotherapy on DTC with TKI. In the SELECT trial, lenvatinib significantly prolonged median progression-free survival (PFS; the primary endpoint) in patients with progressive RAI-refractory DTC, compared with those on placebo. In one study, the response rate of lenvatinib was found to be 64.8%, while the median response time was 2.0 months [5]. This short response time and high response

rate suggests that lenvatinib is a good candidate for neoadjuvant chemotherapy in DTC.

It is well known that the inhibition of blood vessel formation via antiangiogenic agents can impair wound healing. Lenvatinib has a median half-life of 35 h; 7 days of withdrawal was required before a major surgery in the SELECT trial. In our case, lenvatinib was discontinued 17 days before surgery and there was no perioperative complication. Perioperative VEGF-targeted therapies can be safe when an appropriate interval period is allowed before surgery.

Fistula formation, although a rare side effect of antiangiogenic TKI, can be life threatening. In our case, there were concerns about a possible formation of an aerodigestive fistula, due to the presence of the tumor adjacent the esophagus and bronchus, as well as bleeding due to the presence of the tumor adjacent the right internal jugular vein. Therefore, the patient was started on lenvatinib 14 mg/day and followed up carefully with frequent CT examinations. After administration of lenvatinib, the tumor in the right lobe of thyroid did not show any remarkable efficacy compared to the metastatic lymph nodes. The reason may have been that the effect of lenvatinib on the thyroid tumor resulted in the formation of a cavity due to internal necrosis of the tumor. We also thought that a progression in the formation of such a cavity might finally lead to the formation of a fistula. Particular caution is needed when lenvatinib is being administered to a patient whose tumor metastasizes into vital structures such as the esophagus, the trachea, and the major blood vessels.

4. Conclusion

In summary, we reported a case of a locally advanced papillary thyroid carcinoma that was resected after preoperative lenvatinib treatment without perioperative complications. For an advanced DTC that requires removal through invasive surgery, preoperative lenvatinib treatment might be one of the options for a less invasive surgery. This case was not placed on a study protocol because of necessity of immediate treatment, However, future studies will need to elucidate the possibilities for neoadjuvant chemotherapy of TKI in advanced DTC.

Disclosure

The authors declare no conflict of interest associated with this manuscript.

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Ethical approval

Not applicable to case report.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Author contribution

Mitsuhiro Tsuboi, MD: Writing manuscript. managing case.
Hiromitsu Takizawa, MD, PhD: managing case.
Mariko Aoyama, MD: managing case.
Akira Tangoku, MD, PhD: managing case.

Guarantor

Mitsuhiro Tsuboi and Hitomitsu Takizawa are Guarantors for this case report.

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