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Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 82926

Manuscript Type: CASE REPORT

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Efficacy of anlotinib combined with radioiodine to treat scalp metastasis of papillary thyroid cancer: A case report and review of literature

Zhang LY *et al.* Neoadjuvant anlotinib therapy for PTC

Li-Yong Zhang, Shao-Jun Cai, Bo-Yan Liang, Shou-Yi Yan, Bo Wang, Meng-Yao Li, Wen-Xin Zhao

Abstract

BACKGROUND

Papillary thyroid cancer (PTC) is one of the well-differentiated thyroid tumors. Cutaneous metastasis from differentiated thyroid cancers occurs in < 1% of primary thyroid carcinomas but produces the worst survival prognosis. The multi-targeting tyrosine kinase inhibitor anlotinib has been approved to treat refractory advanced non-small-cell lung cancer as well as advanced soft-tissue and clear cell sarcomas in China.

CASE SUMMARY

In a patient with scalp metastasis caused by PTC, thyroid and skull metastasis tumor sizes were significantly reduced after a trial of neoadjuvant anlotinib therapy for 3 cycles. Anlotinib maintenance medication after thyroidectomy further reduced the metastatic skull tumor size thereby preventing the requirement for craniotomy.

CONCLUSION

The outcome of the present trial confirmed the potential of anlotinib therapy to treat scalp metastasis induced by PTC and point the way for the treatment of similar diseases in the future.

Key Words: Papillary thyroid cancer; Tyrosine kinase inhibitor; Neoadjuvant anlotinib therapy; Literature review; Case report

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Zhang LY, Cai SJ, Liang BY, Yan SY, Wang B, Li MY, Zhao WX. Efficacy of anlotinib combined with radioiodine to treat scalp metastasis of papillary thyroid cancer: A case report and review of literature. *World J Clin Cases* 2023; In press

Core Tip: Cutaneous metastasis to the scalp is a site in patients which occurs after papillary thyroid cancers (PTC). Tyrosine kinase inhibitors represent a new approach to treat certain types of thyroid cancer. Here we report a case of scalp metastasis caused by PTC, in which neoadjuvant therapy of anlotinib before thyroidectomy was beneficial in reducing the thyroid and skull metastasis tumor sizes. Anlotinib maintenance regimen after thyroidectomy reduced the size of the metastatic skull tumor further, which successfully avoided the need for craniotomy.

8 INTRODUCTION

Papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) are the two most common differentiated thyroid tumors (DTC)^[1,2], with lymph nodes metastasis occurring frequently, but also cutaneous metastasis to the scalp being a common site. The average survival time for patients with thyroid carcinoma skin metastasis was about 19 mo from the end of the last century^[1]. Most patients with thyroid cancer undergo surgery combined with subsequent radioactive iodine (RAI) therapy to clear any remaining tumor tissue and to prevent thyroid cancer recurrence^[3]. RAI therapy is also given for more advanced cancers and/or cancers that have spread to lymph nodes or distant areas^[4]. Apart from these regular treatment regimens, novel target therapies including a tyrosine kinase inhibitor (TKI) has become a new approach to treat certain types of thyroid cancer

For example, sorafenib⁵ was approved by the United States Food and Drug Administration (FDA) in 2014 for the treatment of radioiodine-resistant differentiated thyroid cancer with metastasis⁴. Anlotinib is a new TKI that targets the vascular endothelial growth factor, fibroblast growth factor and platelet-derived growth factor receptors as well as c-kit⁶. Anlotinib was approved as third-line therapy for refractory advanced non-small-cell lung cancer in 2018, and as second-line treatment for advanced soft-tissue and clear cell sarcomas in 2019 in China⁷. In a preclinical study, anlotinib inhibited the cell viability of PTC, suppressed migration of thyroid cancer cells *in vitro* and also xenograft thyroid tumor growth in mice². In a phase 2b study of medullary thyroid cancer patients treated with anlotinib, the median progression free survival (PFS) was found to be significantly prolonged (20.7 *vs* 11.1 mo)⁹. Another recent case of a patient with recurrent and metastatic radioactive iodine-refractory DTC treated with anlotinib showed a partial response after 2 cycles of anlotinib treatment and a PFS time of 37 mo¹⁰.

³ **CASE PRESENTATION**

Chief complaints

A 72-year-old woman presented to our hospital with a scalp mass on November 3, 2020.

History of present illness

A scalp mass biopsy puncture indicated that thyroid cancer metastasis.

¹ *History of past illness*

The patient had no previous history of any illnesses.

Personal and family history

The patient had no previous personal and family history.

Physical examination

On December 4, 2020, a 3.0 cm × 3.0 cm nodule was palpable on the left thyroid and a 4.0 cm × 3.0 cm nodule was palpable on the right thyroid. In addition, a 6.5 cm × 5.0 cm mass was palpable in the left temporoparietal junction region.

Laboratory examinations

Immunohistochemical results: TTF-1 (+), CK7 (+), NapsinA (+), CDX-2 (-).

Imaging examinations

A scheme of the diagnoses and treatments in chronological order is provided in Figure 1. On November 16, 2020, a positron emission tomography-computed tomography (PET-CT) imaging diagnosis was conducted in which a hypermetabolic mass was revealed in the left parietal skull bone, indicating skin metastasis (Figure 2A), which was confirmed by a fine-needle aspiration biopsy diagnosis (Figure 2B). In addition, a bilaterally enlarged thyroid gland with increased metabolism was found (Figure 2C).

Lung CT was performed on November 26, 2020, which revealed ground glass nodules at the posterior end of the right upper lung lobe and in the dorsal portion of the right lower lung lobe. The ground glass nodules observed at the posterior end of the right upper lobe may correlate with the possibility of primary lung adenocarcinoma and oblique fissure. Both lungs exhibited scattered ground glass patches, likely due to chronic inflammation.

On January 19, 2021, A thyroid color ultrasound image revealed a left thyroid nodule with calcification (Chinese TI-RADS category 4) and a right thyroid nodule with calcification (Chinese TI-RADS category 3c)^[11] (Figure 3).

FINAL DIAGNOSIS

According to the findings, bilobed PTC with scalp and skull metastasis was diagnosed based on histopathology data and PET-CT imaging. Next-generation sequencing (NGS) by ¹⁰an Illumina Novaseq 6000 system (Illumina, San Diego, CA, United States) revealed mutations in the BRAF, KRAS and IGF1R genes of the PTC. In addition, neck metastasis of the PTC and primary lung cancer were provisionally diagnosed.

TREATMENT

On November 30, 2020, a thoracoscopic radical resection of the right upper lung cancer (resection of the posterior segment of the right upper lung + mediastinal lymph node sampling) plus wedge resection of the right lower lung were carried out. The operation went without complications and the postoperative recovery of the patient was good.

On January 19, 2021, the patient was given the first oral dose of anlotinib in 3-wk cycles of 12 mg qd during the first 2 wk and 1-wk off (Figure 3B). After 3 cycles of anlotinib treatment, the skull tumor size was significantly reduced. The nodule palpated on the left thyroid gland became 3.0 cm × 2.0 cm, and the nodule palpated on the lower part of the right gland became 4.0 cm × 2.0 cm. In addition, preoperative color ultrasonography also showed that the thyroid tumor size was significantly reduced after neoadjuvant anlotinib therapy (Figure 3E).

A thyroidectomy was performed on March 17, 2021 with the left thyroid lobule and isthmus and the right thyroid lobule and lymph nodes in the central region

successfully removed. The histopathology confirmed PTC (Figure 2D). Targeted maintenance therapy of anlotinib was administered after the operation in order to avoid craniotomy (Figure 3C).

OUTCOME AND FOLLOW-UP

By postoperative day 2 (March 18 2021), the neck incision had healed and the patient recovered well. The intact parathyroid hormone concentration was 1.10 pmol/L and the electrolytic calcium concentration was 2.21 mmol/L.

Once iodine-131 therapy (dosage: 150 mci) was performed after the operation on May 18, 2021 and continued in combination with anlotinib (currently in the 11th cycle), a regimen which successfully avoided the need for craniotomy.

DISCUSSION

The 4 main subtypes of thyroid carcinoma are papillary, follicular, medullary and anaplastic forms^[12], with PTC being the most frequently occurring followed by FTC^[13,14]. In this case report, the potential of anlotinib therapy to treat scalp metastasis induced by PTC was demonstrated. Scalp metastasis of thyroid cancer has been also been described in other case reports^[15-22] (Table 1). Most of the patients were females of advanced age with follicular TC and in the majority of the cases the skull metastasis had been diagnosed before TC, as in the present case. Only 2 patients received post-operative TKI medication and the lung was the major organ of cancer lesions, which were supposed to be metastatic (Table 1). TKIs are small molecules which inhibit the activity of tyrosine kinases (Figure 4).

TKI therapy is usually the final option for metastatic lesions, which are normally incurable by surgery and/or RAI therapy combined, but encouragingly a study involving 147 patients demonstrated that TKI treatment improved the

prognosis of patients with distant metastasis and progressive disease^[23]. A number of TKIs have been approved by the FDA to treat thyroid cancer, including vandetanib, cabozantinib, sorafenib and lenvatinib (Table 2). Vandetanib and cabozantinib were the first and second approved drugs for the therapy of advanced and progressive and/or symptomatic medullary thyroid cancer^[24,25]. Sorafenib was approved for the treatment of ¹³¹I-refractory DTC after the findings of the phase 3 DECISION clinical trial^[26]. Lenvatinib is an anti-angiogenic TKI that has been approved for the treatment of advanced and progressive ¹³¹I- refractory DTC^[27]. A real-world study conducted in the United States demonstrated that treatment with first-line lenvatinib followed by subsequent second-line therapy delivered a clear clinical benefit^[28]. A study carried out in Korea mainly focused on the adverse events of TKIs (lenvatinib and sorafenib) elicited in patients with DTC. Seventy-one cases (lenvatinib, *n* = 23; sorafenib, *n* = 48) were involved without new safety concerns being identified for either drug. Most AEs were managed with dose modification and medical therapy^[29]. In former *in vitro* experiments, anlotinib reduced the viability of PTC and ATC cell lines, most likely due to aberrant spindle assembly, G2/M arrest and TP53 activation, while in a murine model anlotinib suppressed migration and growth of thyroid tumor xenografts^[8]. Recently, a phase 2 trial of anlotinib in Chinese patients with radioiodine-refractory DTC showed promising results with a median PFS time of 40.54 mo in the treatment group compared to 8.38 mo in the placebo group at a data cutoff date of January 2020^[30].

Nevertheless, the present case report can be considered as a kind of pilot study. Besides conservative treatments, anlotinib has been used as neoadjuvant therapy, which significantly reduced the sizes of a metastatic skull tumor and of the primary PTC, while in combination with anlotinib maintenance medication a craniotomy was avoided.

NGS analysis of the PTC found mutations in the *BRAF*, *KRAS* and *IGF1R* genes, which did not match with the previously described undifferentiated thyroid cancer specific mutations of the *TERT* promoter, *RET* fusion and *TP53*^[31]. On the other hand, *BRAF* mutations have been found to be key drivers of differentiated thyroid cancer (DTC), leading to the proposal of BRAF-directed therapies^[32]. In line with the findings of the present study, a recent case report found that anlotinib was effective for the treatment of a radioactive iodine-refractory DTC (RIR-DTC) patient with *TERT* promoter and *BRAF* mutations^[10]. Another case report of a RIR-DTC PTC patient with a *BRAF*^{V600E} mutation noted that the patient developed tumor progression, with clinical symptoms that worsened after dabrafenib-trametinib withdrawal^[33]. In our case we will continue to monitor the outcome of anlotinib maintenance therapy.

A limitation of the present study was the lack of NGS and histopathology data about the lung lesions and the neck lymph nodes, which had been provisionally diagnosed as primary lung cancer and PTC metastasis into the neck.

CONCLUSION

Neoadjuvant therapy of anlotinib before surgery was beneficial in reducing the thyroid tumor volume, but also that of the metastatic skull tumor. A craniotomy was thus avoided by using anlotinib maintenance therapy. Our findings point the way for the treatment of similar diseases in the future.

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