

CASE REPORT

Satisfactory short-term outcome after anlotinib and docetaxel chemotherapy in tongue cancer with N3 cervical lymph node metastasis: A case report

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Abstract

Patients with tongue squamous cell carcinoma (TSCC) and cervical lymph node metastasis are particularly difficult to treat. This is the first report of about anlotinib combined with docetaxel chemotherapy for chemotherapy-refractory TSCC with cervical lymph node metastasis, may provide a new, suitable therapeutic option for these patients.

KEYWORDS

anlotinib, antiangiogenesis, cervical lymph node metastasis, docetaxel, tongue squamous cell carcinoma

1 | INTRODUCTION

The current standard treatment for patients with early-stage (clinical tumor classification cT1-T2, N0) tongue squamous cell carcinoma (TSCC) is primary excision. However, patients with cervical lymph node metastasis are particularly difficult to treat, especially when cervical lymph node metastases exceed 6 cm (N3), which commonly led to a poor prognosis.¹ Traditionally, docetaxel-based regimens, intraarterial chemotherapy, and radiotherapy with cetuximab are the standard treatment modalities to achieve definitive management of locoregionally advanced TSCC of the head and neck.² However, for TSCC patients with cervical lymph node metastasis, the results of current treatments remain unsatisfactory. It is important to explore a new treatment strategy for TSCC patients with cervical lymph node metastasis in order to improve its prognosis.

Anlotinib is a novel oral multi-targeted receptor tyrosine kinase inhibitor that inhibits vascular endothelial growth factor receptor (VEGFR) 1-3, fibroblast growth factor receptor (FGFR) 1-4, platelet-derived growth factor receptors

(PDGFR) α/β , c-Kit, and Met.³ Anlotinib has been used in a wide range of tumor types, including renal carcinoma, soft tissue sarcoma, medullary thyroid carcinoma, nonsmall cell lung cancer, colorectal cancer, melanoma, thymic carcinoma, and adenoid cystic carcinoma. To our knowledge, there has been no report of anlotinib combined with docetaxel chemotherapy in TSCC patients with N3 cervical lymph node metastasis.

Herein, we present a case of a 74-year-old man who had recurrent TSCC with N3 cervical lymph node metastasis after initial surgical resection and chemotherapy. After failed traditional chemotherapy, we treated the patient with anlotinib and docetaxel chemotherapy. The patient experienced a favorable short-term outcome after this treatment strategy.

2 | CASE REPORT

A 74-year-old patient came to our hospital with the chief complaint of a tongue lesion. The patient experienced pain when he moved his tongue and while eating. There were

poorly healing aphthae on the left side of the tongue for several months before the presentation of current symptoms. He had no known allergies and was not on any medicine. He had smoked 2-3 cigarettes per day for 8 years but denied chronic alcohol abuse. Upon examination, the patient showed a symmetrical face and a normal skin color. The motor and sensory cranial nerve functions were intact. No lymph node was palpable on either side of his neck.

Upon intraoral examination, we found a nodule in the middle third position of the left side of the tongue. Magnetic resonance imaging (MRI) demonstrated that the size of the tongue lesion was about 13 × 31 mm, and it appeared exophytic, with a central ulcer infiltrating into the tongue musculature that seemed to be relatively well demarcated

(Figure 1A). A biopsy under local anesthesia was performed. Histopathology examination showed a moderately differentiated squamous cell carcinoma with surrounding chronic inflammation (Figure 2A). No evidence of locoregional lymphatic spread or distant metastasis was found. Therefore, we concluded that the tumor was at stage cT1N0M0.

After the examination, an extended glossectomy was conducted. Histological examination confirmed the presence of a highly differentiated TSCC of the left side of the tongue and invasion of skeletal muscle (Figure 2B, 2C). Postoperatively, the patient declined any chemoradiotherapy. Unfortunately, 8 months later, he presented to our hospital again, with 75 × 60 × 82 mm cervical lymph nodes, and physical examination showed that the nodule had a hard texture,

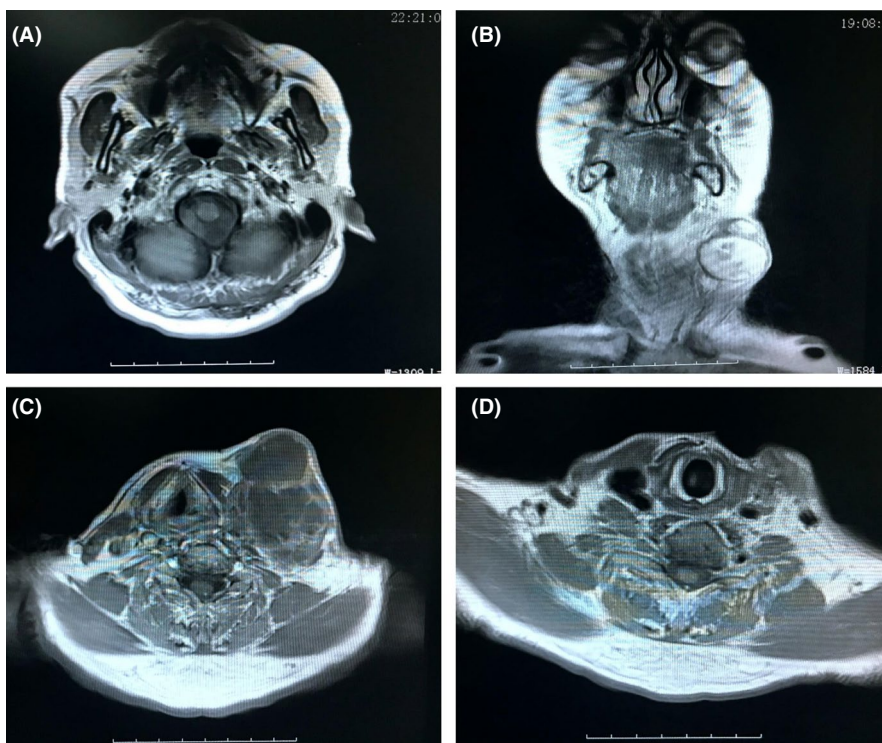


FIGURE 1 A, The initial Magnetic resonance imaging (MRI) indicated that the lesion on the tongue was markedly enhanced before surgery. B, MRI showed a significantly enlarged lymph node in the left neck after 12 mo; C, MRI revealed the lesion has not changed after four circles of chemotherapy; D, MRI examination showed the swollen lymph nodes significantly narrowed and the border was not clear, suggesting that the patient achieved a partial response after two weeks of therapy with anlotinib

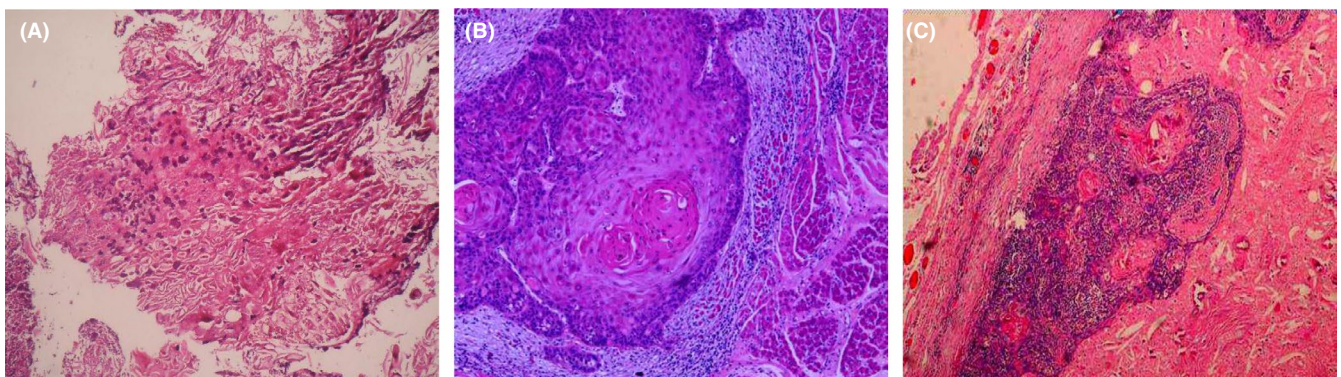


FIGURE 2 Histological hematoxylin and eosin analysis of oral tongue squamous cell carcinoma. A, Preoperative pathology suggested tongue squamous cell carcinoma; B, Postoperative pathology revealed tongue squamous cell carcinoma, which invaded skeletal muscle; C, Biopsy revealed cervical metastasis of tongue cancer. (Hematoxylin and eosin stain, [A, B] 200× magnification, [C] 100× magnification)

FIGURE 3 Visual inspection of cervical lymph node metastasis. A, Post-traditional chemotherapy (docetaxel + cisplatin) the size is about $75 \times 60 \times 82$ mm; B, Postnovel chemotherapy (anlotinib + docetaxel) the size is $35 \times 31 \times 21$ mm

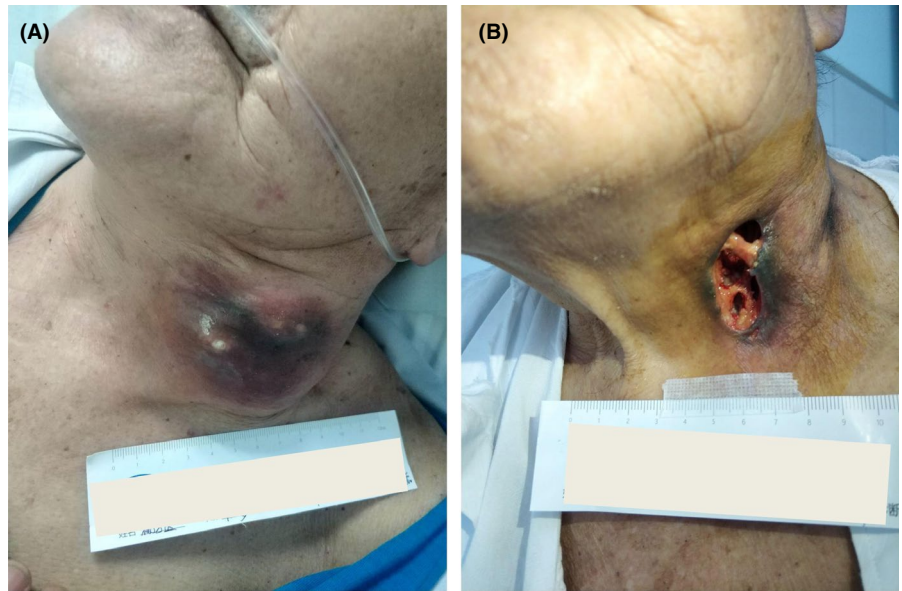


FIGURE 4 Treatment schedule

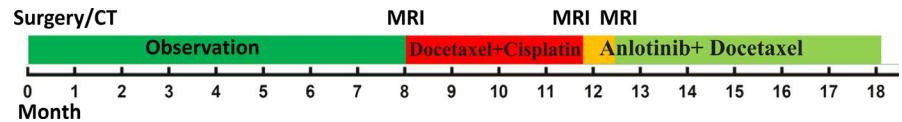


TABLE 1 Changes of tumor sizes and lymph nodes after surgery or chemotherapy

Time course	Tongue lesion (mm)	Cervical lymph node metastasis (mm)
Initial hospital presentation (Month 0)	13 × 31	None
Second hospital presentation (Month 8)	None	57 × 48 × 53
Post-traditional chemotherapy (docetaxel + cisplatin, Month 12)	None	75 × 60 × 82
Postnovel chemotherapy (anlotinib + docetaxel, Month 12.5)	None	35 × 31 × 21

unclear boundary, and a low degree of mobility (Figure 3A). The MRI (Figure 1B) and biopsy indicated cervical lymph node metastasis of tongue cancer (Figure 2D). This patient underwent four cycles of chemotherapy (docetaxel 75 mg/m^2 , cisplatin 75 mg/m^2), with no change observed to the lesion (Figure 1C).

The Institutional Ethics Review Board of our hospital approved the study, and the patient submitted written informed consent, including publication of the case details. Anlotinib (at a dose of 12 mg, once daily, 2-weeks on/1-week off), was added to docetaxel for this patient (Figure 4). To our surprise, after treatment for two weeks, the lesion was reduced on visual inspection (Figure 3B). The size of the tongue lesion was reduced to $35 \times 31 \times 21$ mm by MRI (Figure 1D; Table 1). The efficacy was evaluated as partial response (PR). No adverse events were observed during treatment (according to the National Cancer Institute's

Common Terminology Criteria for Adverse Events, version 4.0).⁴

3 | DISCUSSION

The most important prognostic factor for oral cancer patients is the presence of neck metastasis, which is associated with a poor prognosis.⁵ Unfortunately, the overall prevalence of nodal metastasis in the neck was nearly 49.5% during the initial clinical visits.^{6,7} Although intraarterial chemotherapy docetaxel and cisplatin have been shown to have a pronounced therapeutic effect on TSCC,^{8,9} many hospitals cannot perform super-selective intraarterial chemotherapy and many patients do not accept this therapy, especially in developing countries. Therefore, alternative treatment option is imperative for our patient.

Anlotinib is a novel TKI targeting the vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), and c-Kit. It was shown to have antitumor activity in squamous carcinoma.^{10,11} Expression of VEGF-C in the primary TSCC was a strong indicator for cervical lymph node metastases.¹² In human OTSCC samples, low MMP-8 in combination with high VEGF-C was an independent predictor of poor cancer-specific survival.¹³ These results showed that anlotinib could have a potent anticancer activity on TSCC cells. Although there are no clinical trial results of anlotinib in TSCC, phase II trials in China are currently conducted to evaluate the safety and efficacy of anlotinib in esophageal squamous cell carcinoma (NCT02649361),¹⁴ which is a similar type of epithelial TSCC.

The results of antiangiogenic drugs combine with docetaxel have been controversial. An in vitro study in China used A549 cells to compare the result of single-drug treatment with the combination treatment of sunitinib (Sutent[®], Pfizer, inhibiting VEGFR-1, VEGFR-2, and PDGF β^{15}) and docetaxel. It was found that cell proliferation inhibition rate, late apoptosis rate, and total apoptosis rate increased in the combination treatment group, and the docetaxel sequential sunitinib group showed higher rates of cell proliferation and apoptosis than the sunitinib sequential docetaxel group. Another study combined treatment of docetaxel with a small-molecule inhibitor of VEGFR-2 (apatinib) in A549 xenograft mice, which significantly enhanced the antitumor effect of docetaxel and alleviated docetaxel-induced liver damage and decreased serum transaminases (ALT and AST) by increasing the docetaxel concentration in tumors and decreased docetaxel-induced upregulation of P-glycoprotein in tumors.¹⁶ In a clinical trial, the objective response rate (ORR) was significantly higher in the combination group (55%) of sunitinib with docetaxel than with monotherapy group (42%; one-sided $P = .001$).¹⁷ In phase II clinical study, anti-human VEGF-A bevacizumab (Avastin[®]) in combination with docetaxel was tolerable and effective in locally advanced squamous cell carcinoma of the head and neck.¹⁸ Through this evidence and our current case, we consider that anlotinib combined with docetaxel can achieve satisfactory clinical outcomes for TSCC.

Even though there is no evidence regarding the safety of the combination of anlotinib with docetaxel chemotherapy, a similar randomized study revealed that the frequency of common adverse events (AEs) was higher with a combination of sunitinib with docetaxel rather than with monotherapy, but only grade 3 or 4 AEs occurred significantly more frequently in sunitinib in combination with another agent than with monotherapy was hand-foot syndrome (17% vs 1%, respectively; $P < .001$).¹⁷ Another study (NCT02072031) showed that anlotinib had a better tolerability profile than sunitinib, and the incidences of the following AEs (any grade) were significantly lower with

anlotinib than with sunitinib ($P \leq .015$).¹⁹ For this reason, we consider that patients with TSCC can tolerate anlotinib combined with docetaxel chemotherapy.

To our knowledge, this is the first case of anlotinib combined with docetaxel chemotherapy significantly reduced swollen lymph nodes for chemotherapy-refractory cervical lymph node metastasis of TSCC. This finding may have potential therapeutic application as clinical trials remain important for patients with tongue cancer, for whom treatment options are extremely limited. Nevertheless, more data and clinical trials are needed.

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CONFLICT OF INTEREST

There are no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

YD: had significant contributions to the conception of the study; to the generation, analysis, and interpretation of the data; and to preparing the manuscript. ZYZ: had significant contributions to the generation and analysis of the data and to preparing the manuscript. XRT and SW: had significant contributions to the analysis and interpretation of the data and to preparing the manuscript. KQ: conducted a critical review of the manuscript and resources. All authors read and approved the final manuscript.

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