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*Case Report*

# Lenvatinib is an effective treatment for refractory nasopharyngeal carcinoma harboring FGFR3-TACC fusion: a case report

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**Abstract:** Background: Molecular targeted therapy is a novel and effective approach to treat some advanced solid tumors. It may also be therapeutic therapy for nasopharyngeal carcinoma (NPC). Case presentation: Herein, we report a patient with refractory NPC who benefited from treatment with Lenvatinib based on the results of next generation sequencing (NGS), which revealed the presence of fibroblast growth factor receptor 3 (FGFR3) and transforming acidic coiled-coil-containing protein (TACC3) gene fusion. Conclusions: Genomic alteration analysis based on NGS may help patients with refractory NPC to find effective therapeutic targets.

**Keywords:** Lenvatinib, nasopharyngeal carcinoma, FGFR3-TACC3 fusion, NGS, molecular targeted therapy

## Introduction

NPC arises from the nasopharyngeal epithelium. About 86,500 incidences of NPC are annually reported worldwide, accounting for 0.6% among all cancers [1]. The distribution of NPC varies in races and geographical areas. NPC occurs commonly in south China and southeast Asia but is rare in Europe and America. Radiotherapy and/or chemoradiotherapy is the standard treatment for local NPC and the 5-years overall survival rate is above 85% [2]. However, there are about 15%-30% of patients who develop local recurrence or distant metastasis, and they are recommended to receive platinum-based doublet chemotherapy. Unfortunately, the outcome is very poor, with a median overall survival ranged from 11.5 to 21.5 months [3, 4].

Molecular targeted therapy has achieved remarkable success in treatment of various solid tumors such as non-small-cell lung cancer, breast cancer, colorectal cancer etc. Currently, clinical studies targeting epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) are also ongoing in NPC [5-7]. Lenvatinib is a multiple receptor tyrosine kinase inhibitor of VEGFR, FGFR, RET, c-Kit etc., and has been approved in several solid tumours. Previous *in vitro* study has shown that the combination of lenvatinib and I-131 displayed a significant inhibitory effect on the growth, apoptosis, migration and invasion of nasopharyngeal carcinoma cells [8]. Besides, most recent research has demonstrated that lenvatinib exhibited obvious antitumor effects in NPC-bearing mice [9]. There are few reports of patients with NPC who benefitted from lenvatinib. Here we report a patient with refractory NPC harbouring FGFR3-TACC gene fusion who responded well to lenvatinib.

## Case presentation

A 60-year-old female patient was admitted to our hospital in September 2016 with a one-month history of rhinobyon accompanied by hemorrhinia and tinnitus. The electronic nasopharyngeal laryngoscope indicated there was a

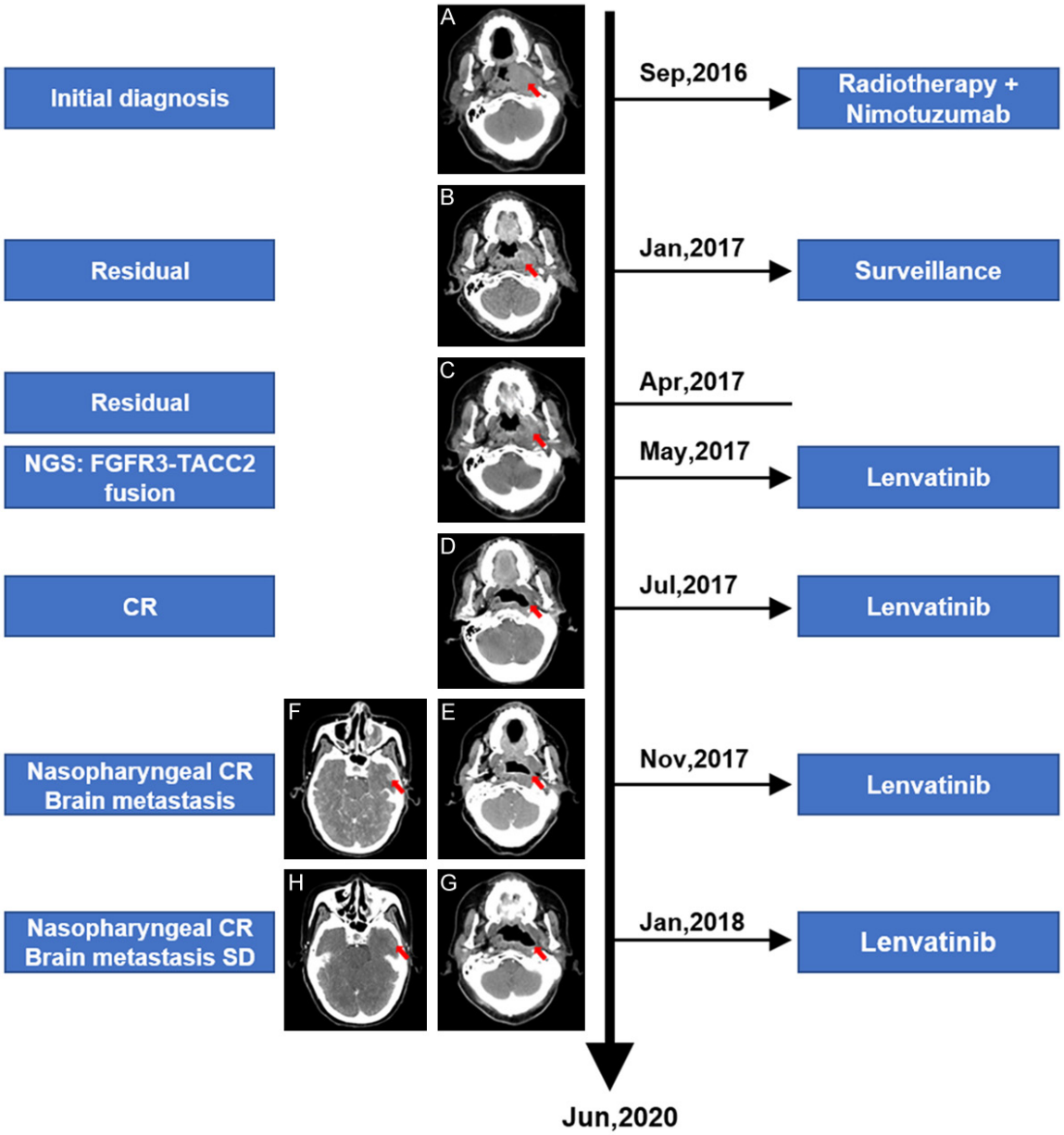


**Figure 1.** The patient's treatment timeline and the corresponding radiological disease evolution. The baseline nasopharyngeal tumor volume was very large (A). Three months after radical radiotherapy and nimotuzumab treatment, there was also a half volume of primary tumor in the nasopharynx and oropharynx (B). Six months after radical radiotherapy, the tumor was still residual (C). According to NGS result, the patient took lenvatinib as off-label treatment to target FGFR3-TACC3 fusion. Tumor in the nasopharynx disappeared after the patient took lenvatinib for 3 months (D). After lenvatinib treatment for 7 months, the patient had a single brain metastasis detected without symptoms but there was no recurrent evidence in the nasopharynx (E, F). The patient continued to be treated with lenvatinib and had both diseases of the nasopharynx and brain (G, H).

neoplasm on the left lateral wall of the nasopharynx. Computed tomography (CT) (**Figure 1A**) and magnetic resonance imaging (MRI) revealed a 5.9×2.7 cm invasive nasopharyngeal mass which infiltrated into the left parapharyngeal space, the left internal carotid, the left medial pterygoid muscle and oropharynx. Pathologic diagnosis of the nasopharyngeal biopsy revealed it was a poorly differentiated squamous cell carcinoma, and confirmed with T3N0M0, stage III, according to the AJCC 8th edition, 2017. Then the patient received defini-

tive radiotherapy with dose of 62 Gy in 31 fractions combined with nimotuzumab (1400 mg divided into seven fractions), which is a monoclonal antibody targeted EGFR and approved by China Food and Drug Administration (CFDA) to treat NPC. CT (**Figure 1B**) was performed 3 months later, and it showed the nasopharyngeal mass size was decreased to 3.2×2.5 cm, indicating the patient had achieved nearly partial response according to the Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST 1.1).

In April 2017, the patient experienced frequent nosebleed, occipital pain, and cephalic edema. CT scan (**Figure 1C**) indicated the nasopharyngeal tumour lesion still existed, while the patient refused chemotherapy, and tumour tissue and peripheral blood samples were subjected to NGS analysis in 3D Medicines Inc., Shanghai, China, a College of American Pathologists (CAP)-certified and Clinical Laboratory Improvement Amendments (CLIA)-accredited laboratory. The genomic profile revealed three somatic mutations, including FGFR3-TACC3 gene fusion (**Figure 2**), KMT2C p.G4665Wfs*18 and APC p.G1288A. Among these mutated genes, there are several TKIs targeting FGFR3 gene mutation, such as pazopanib, ponatinib and lenvatinib. From May 2017, the patient received lenvatinib 24 mg oral daily and meanwhile provided off-label treatment approval.

One month after lenvantinib treatment, slight headache was reported and no other serious adverse events were observed. Then CT scan (**Figure 1D**) indicated soft tissue around the gross tumor volume area that was a little thicker but the nasopharyngeal mass had disappeared. In July 2017, it was assessed as complete response (CR) after lenvatinib treatment. CT scan performed in November 2017 (**Figure 1E**) showed nasopharyngeal disease was still stable. Meanwhile, cranial CT scan revealed that there was a left temporal lobe tumor in the brain (maximum diameter: 1.3 cm) (**Figure 1F**). Stereotactic Ablative Radiotherapy (SABR) was recommended but the patients refused, therefore, treatment of lenvatinib was continued. In January 2018, CT (**Figure 1G**, **1H**) showed both the nasopharyngeal tumor and the brain metastatic tumor remained as stable disease (SD). Karnofsky score increased from 60 at brain metastasis presence to 90 at SD, and The Eastern Cooperative Oncology Group (ECOG) decreased from 3 to 1. After that, we lost some follow-up information, and learned that she progressed suddenly in June 2020 and died a few days later.

## Discussion

Although NPC is very sensitive to radiotherapy and platinum chemotherapy, the treatment for the refractory NPC is limited at present. The clinical activity and an acceptable safety of cetuximab in combination with carboplatin were demonstrated several years ago [5]. This may inspire the exploration of more effective molecular targeted therapies for patients with NPC.

The genomic landscape research supply a chance to understand the molecular profile of NPC. There are some frequently altered genes in NPC patients, and these may have the potential to used for targeted therapy such as JAK2, AKT2, PTEN, PIK3CA, FGFR2, ERBB2, etc. [10]. In our case, the patient harboured FGFR3-TACC3 fusion, which was also detected in esophageal squamous cell carcinoma and lung cancer, but only one study reported that FGFR3-TACC3 fusion was detected in NPC in a Chinese patient. The authors used RNA-sequencing to detect specimens of 159 NPC patients and found 4 (2.5%) patients harboured FGFR3-TACC3 fusion. The study confirmed that FGFR3-TACC3 fusion gene promoted cell proliferation, colony formation, and transforming ability in NPC cell lines and could be abrogated by FGFR inhibitor [11].

Lenvatinib is an antiangiogenic agent, similar to pazopanib, and sorafenib etc. Lim WT and his colleague reported on the clinical activity and safety of pazopanib in patients with metastatic or recurrent nasophayngeal carcinoma who failed at least one line of chemotherapy [7]. Other researchers explored the activity of sorafenib combined with cisplatin and 5-fluorouracil treatment in 54 chemotherapy-naive patients with metastatic or recurrent nasopharyngeal carcinoma [12]. Lenvatinib is approved for the treatment of radioiodine-refractory differentiated thyroid cancer [11, 13], hepatocellular carcinoma [14], and it is also approved in combination with everolimus for the treatment of advanced renal cell carcinoma.

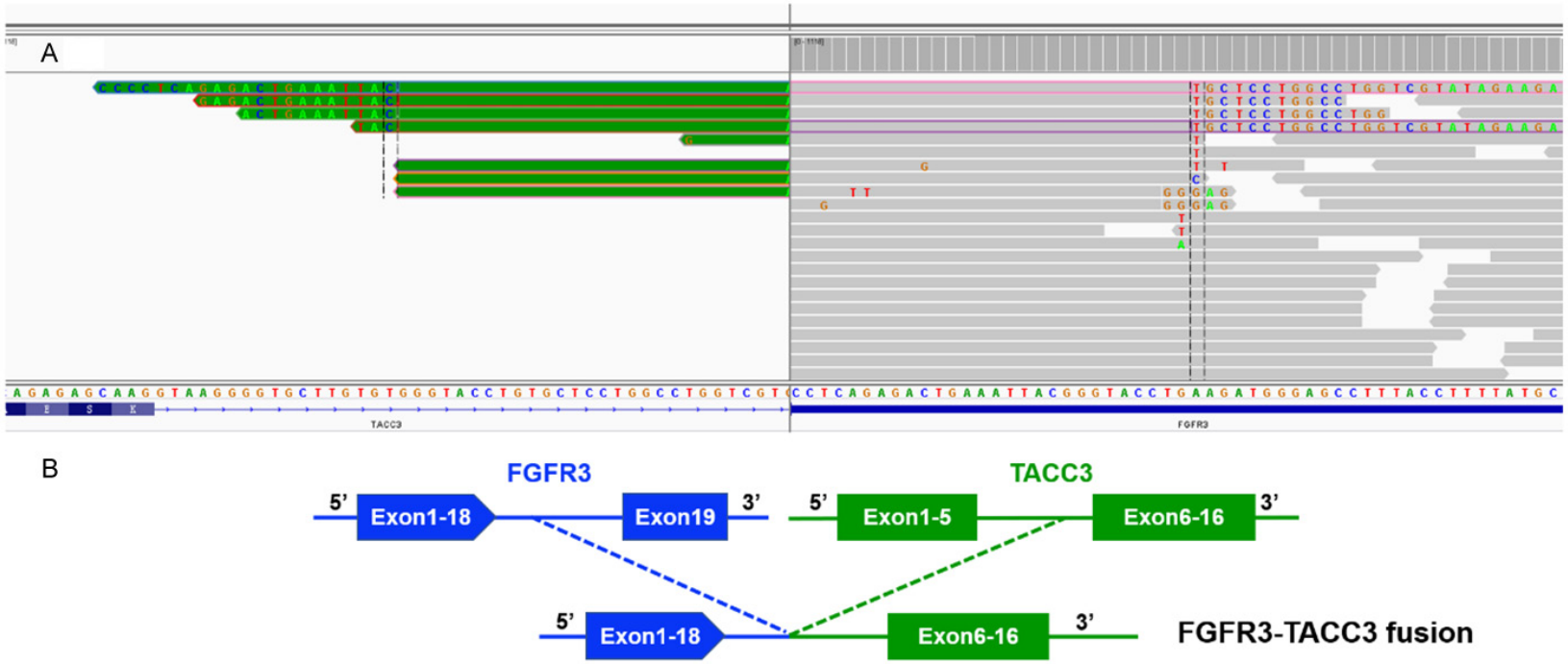


**Figure 2.** Next-generation sequencing findings in the tumor tissue of the patient with nasopharyngeal carcinoma. A. FGFR3-TACC3 fusion was validated manually using the Integrated Genomics Viewer (IGV); B. Illustration of the FGFR3-TACC3 fusion. The exon 1 to exon 18 of FGFR3 were fused with exon 6 to exon 16 of TACC3.

In our case, the patient harboured FGFR3-TACC3 fusion which can activate the FGFR kinase signal and be associated with the development of NPC. As we expected, lenvatinib displayed good local disease control efficacy in the patient. Unexpectedly, she developed a single brain metastasis after 7 months responding to lenvatinib. Although the efficacy of lenvatinib in patients with brain metastases has not been proven, the patient continued treatment of lenvatinib for her own reasons. However, pre-clinical study has shown that lenvatinib can cross the blood-brain barrier, and the research has shown that the distribution of lenvatinib in cerebrospinal fluid is 2-14% of plasma [15]. Continuous treatment of lenvatinib and subsequent stable disease both in the nasopharyngeal disease and the brain metastatic disease may also demonstrate the moderate intercranial effect of lenvatinib to a certain extent.

## Conclusion

Molecular targeted therapy is a promising treatment option for refractory NCP, which deserves more exploration and research. NGS can be considered as a routine test to explore more opportunities for treating refractory NCP.

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## Disclosure of conflict of interest

None.

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