

Apatinib monotherapy for advanced VEGFR-2-negative nasopharyngeal carcinoma

A case report

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Abstract

Rationale: Due to the anatomical and biological characteristics of nasopharyngeal carcinoma (NPC), radiotherapy is the standard treatment of choice. Recent advances in small molecule therapies targeting tumor angiogenesis also hold promise for the treatment of advanced NPC.

Patient concerns: The patient's symptoms, including nasal obstruction, nasal bleeding, and headache, reappeared periodically and eventually became so severe that the patient's vision became impaired. In January 2016, the patient presented with blurred vision, diplopia, language impairment, left temporal paralysis, and bilateral eyelid ptosis.

Diagnosis: Advanced NPC without metastasis in a 55-year-old man.

Interventions: The patient refused treatment with radiotherapy or chemotherapy and was treated with Chinese herbal medicines. Following a worsening of symptoms, the patient was subsequently treated with apatinib monotherapy (0.25 g, once daily).

Outcomes: Symptom improvement, including decreased nasal bleeding and headache, was observed after 1 week of apatinib treatment. After 100 days of treatment, the patient was nearly asymptomatic with stable disease and improved quality of life.

Lessons: For patients with advanced NPC who refuse standard radiotherapy and chemotherapy, apatinib monotherapy may be a suitable treatment option to improve symptoms and quality of life even in those with vascular endothelial growth factor receptor-negative tumors.

Abbreviations: ECOG = Eastern Cooperative Oncology Group, EGFR = epithelial growth factor receptor, MRI = magnetic resonance imaging, NPC = nasopharyngeal carcinoma, OS = overall survival, TKI = tyrosine kinase inhibitor, VEGF = vascular endothelial growth factor, VEGFR-2 = vascular endothelial growth factor receptor 2.

Keywords: apatinib, nasopharyngeal carcinoma, quality of life, symptoms

1. Introduction

Approximately 86,500 new cases of nasopharyngeal carcinoma (NPC) are found each year worldwide,^[1] with most cases

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A case report is a medical/educational activity that does not meet the Department of Health and Human Services definition of "research," which is: "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge." Therefore, the activity does not require review and approval by a Johns Hopkins Medicine Institutional Review Board. The patient provided signed informed consent for his data to be analyzed and reported.

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observed in Asia.^[2] Because of the anatomical and biological characteristics of NPC, radiotherapy, especially intensity modulated radiotherapy, remains the treatment of choice.^[3] For those patients with advanced NPC, comprehensive multidisciplinary treatment typically consists of radiotherapy plus chemotherapy.^[3] However, the 5-year overall survival (OS) rates are as low as 28% for those with stage IV disease.^[2] For those with distal metastasis, chemotherapy with prior or simultaneous palliative radiotherapy of the metastatic lesions is often employed.^[2]

In addition to radiotherapy and chemotherapy, targeted drugs have been developed that inhibit tumor angiogenesis,^[4] including cetuximab, gefitinib, erlotinib, sorafenib, nimotuzumab, and bevacizumab. However, no effective drug for the targeted therapy of NPC is available at present. Apatinib is another small molecule tyrosine kinase inhibitor (TKI) that is highly selective for vascular endothelial growth factor receptor 2 (VEGFR-2) with antiangiogenesis properties in vivo.^[5] Apatinib has been used clinically for some advanced cancers, including advanced pancreatic liposarcoma,^[6] gastric cancer,^[7] liver cancer,^[8] angiosarcoma,^[9] nonsmall cell lung cancer,^[10,11] and advanced lung adenocarcinoma,^[12,13] with a favorable safety profile and demonstrated efficacy. However, the efficacy of apatinib in NPC is unknown.

Here, we report the outcomes of a patient with locally advanced NPC treated with apatinib mesylate, achieving favorable efficacy. This may be the first clinical case of advanced NPC in which symptoms were alleviated by apatinib monotherapy alone.

2. Case report

A male patient aged 55 years was admitted to the Dongguan People's Hospital due to nasal obstruction and diagnosed with NPC in 2010. Although the patient refused radiotherapy, he was treated with Chinese medicinal herbs (150g/d; centipede, Tianlong, Herba Hedyotis, *Centipeda minima*, *Agkistrodon* spp., and *Scutellaria barbata*) prepared in beverage form. His symptoms, including nasal obstruction, nasal bleeding, and headache, reappeared periodically and eventually became so severe that the patient's vision became impaired. In January 2016, the patient presented with blurred vision, diplopia, language impairment, left temporal paralysis, and bilateral eyelid ptosis (Fig. 1). In March 2016, magnetic resonance imaging (MRI) confirmed a diagnosis of NPC with involvement of the surrounding tissues, including the posterior nasal passage, bilateral Eustachian tubes, levator palate, circumflexus palate, orbital apex, nasal septum, wing sinus, basilar clivus, left cavernous sinus, and left temporal dura (Fig. 2). In addition,

compression of the left temporal lobe was detected (Fig. 2). No metastasis was detected. Nasal biopsy and pathological examination showed nonkeratinizing cancer (undifferentiated), and immunohistochemistry analysis revealed that the tissues were negative for VEGFR-2. Radiotherapy was considered inadvisable because of the large size of the tumor and the potential for invading the base of the skull and the intracranial nerve. Instead, because the risk of possible damage to normal tissue by radiotherapy was likely to result in adverse consequences, palliative chemotherapy was recommended. However, the patient and his relatives refused chemotherapy. He was, therefore, treated with Huachansu tablets (2 tablets, thrice daily) for more than 2 months. On July 1, 2016, the patient was readmitted due to nasal obstruction, dyspnea, headache, left vision loss, right blurred vision, and diplopia. Physical examination showed apparent malnutrition, unstable walking, buccal respiration, the presence of black blood in the nose, complete ptosis of the left eyelid, vision loss in the left eye, incomplete ptosis of the right eyelid, blurred vision in the right



Figure 1. Examination of the patient's eye showed bilateral eyelid ptosis on July 2016 that was improved with apatinib treatment as shown in the images taken on September 2016 and April 2017.

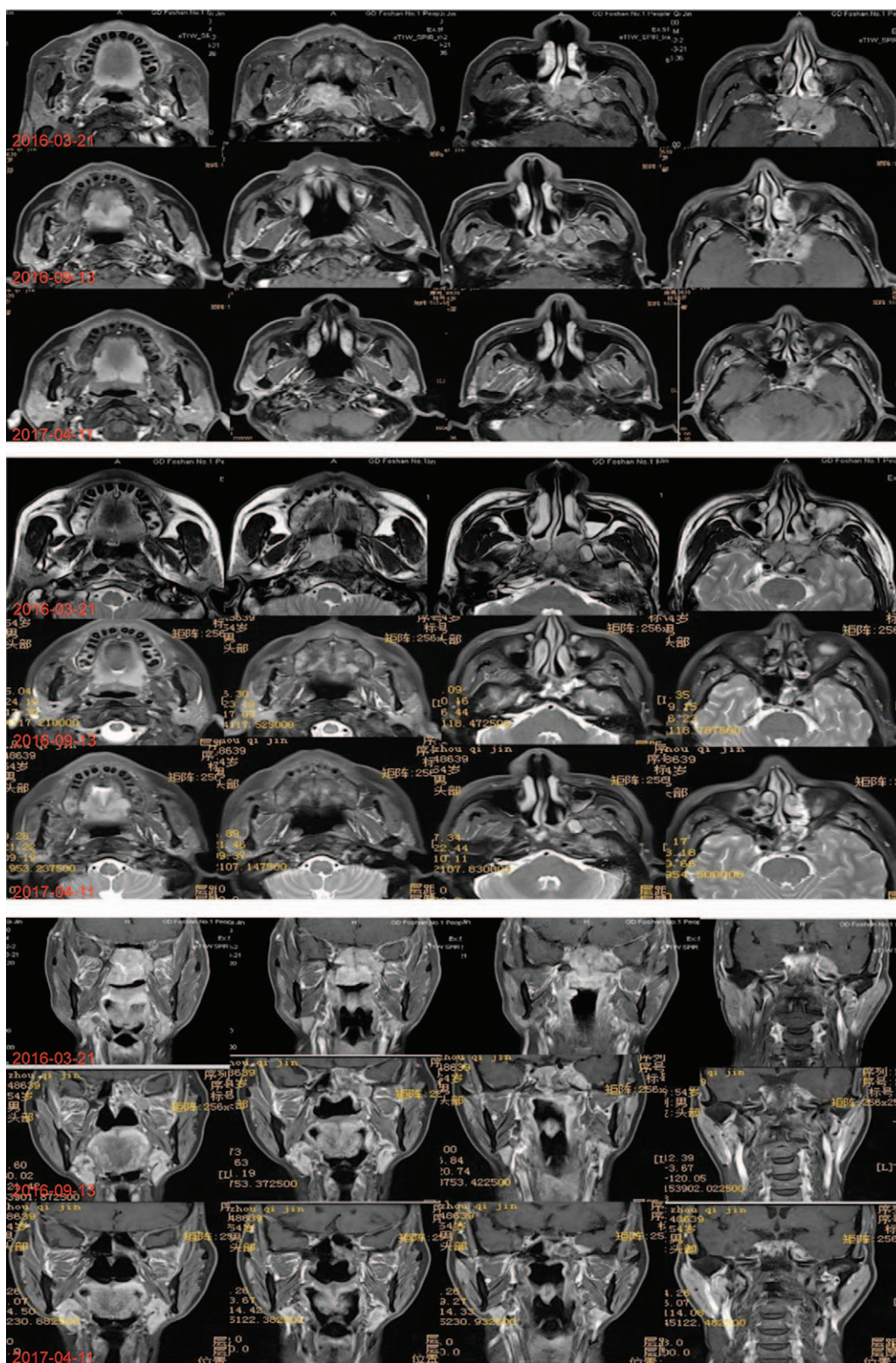


Figure 2. Magnetic resonance imaging of the patient with nasopharyngeal carcinoma on March 2016 (top panels), September 2016 (middle panels), and April 2017 (bottom panels).

eye, and diplopia (Fig. 1). The patient had an Eastern Cooperative Oncology Group (ECOG) score of 4.

Beginning July 4, 2016, the patient was treated with apatinib 0.25 mg, once daily. After 1 week following treatment initiation,

the nasal bleeding improved, massive necrotic tissues were shed, and nasal obstruction and headache were improved. After 2 weeks, the nasal bleeding stopped completely. After 1 month, the patient complained of mild nasal obstruction; however, nasal

Table 1
Symptom improvement with apatinib over time.

Days after apatinib initiation	Symptoms
1 wk	Reduced nasal bleeding Shedding of nasal necrotic tissues Improvements in nasal obstruction and headache
2 wk	Nasal bleeding stopped
1 mo	Free movement in the right eyelid Mildly impaired vision in the right eye Diplopia was absent
40 d	Normal vision in the right eye Partial opening of the right eyelid
70 d	Left diplopia Improved spirit Have the ability of living independence
100 d	Free movement of both eyelids Clear vision in the right eye Mild diplopia in the left eye

bleeding was absent, his right eyelid moved freely, and his vision was improved without diplopia. However, the symptoms of the left eye remained, and left temporal numbness and mild headache were noted. Moderate hand–foot syndrome was also observed. After treatment for 40 days, the patient did not report any headache, and his right vision had improved. In addition, his left eye was able to open, although incompletely, and left vision loss remained. After treatment for 2 months, left temporal numbness remained; his left eye opened incompletely with blurred vision and diplopia was noted. However, he was able to walk freely, the hand–foot syndrome was improved, his appetite was good, and urination and defecation were normal. After treatment for 70 days, left eyelid movement and left vision were improved; however, diplopia, nasal speech, and mild left temporal numbness remained. The patient's spirit was improved to the extent that he could independently care for himself, and he had an improved ECOG score of 2. A second MRI on September 14, 2016 showed that the lesion was reduced significantly. After treatment for 100 days, bilateral eyelid movement was recovered and his right vision was clear (Fig. 1). Although mild left diplopia was noted, the patient could walk freely and had no hand skin lesions, and had normal appetite, urination, defecation, and blood pressure. The patient's ECOG score further improved to 1. After treatment, MRI analysis showed the lesion gradually reduced over time. The most recent MRI analysis in April 2017 showed no further changes in left nasopharyngeal lesions and basilar tumor invasion, suggestive of disease stabilization. (The summary of symptom improvements was shown in Table 1.)

3. Discussion

Apatinib is a targeted therapy that inhibits tumor angiogenesis by targeting VEGFR-2.^[14] The drug may also inhibit some tyrosine kinases, such as platelet-derived growth factor receptor- β (PDGFR- β), c-Kit, Ret, and c-src,^[15,16] by suppressing the proliferation, migration, and microtubule formation of cancer cells. In clinical practice, apatinib has been used for treating advanced cancers.^[6,10–14,17] However, no study has investigated the efficacy of apatinib in treating NPC. For the patient with advanced NPC presented in this case report, apatinib monotherapy alone was sufficient to ameliorate symptoms, leaving only moderate hand–foot syndrome.

In the targeted therapy of advanced NPC, inhibitors of epithelial growth factor receptor (EGFR) are commonly employed given that EGFR expression is often detected in most solid tumors, affecting the proliferation, invasion, and metastasis of cancer cells. High EGFR expression has been noted in about 80% to 90% of patients with NPC.^[18] Cao et al^[19] followed 127 patients with advanced NPC and found that the 5-year OS and 5-year disease-free survival (DFS) were better in patients with EGFR-negative tumors than in those positive for EGFR. Similarly, a meta-analysis by Ooft et al^[20] confirmed that EGFR overexpression predicts the OS and DFS of NPC patients. Thus, EGFR may represent a reliable biomarker for predicting the prognosis of NPC patients as well as an ideal target in the treatment of NPC. However, although EGFR monoclonal antibodies and TKIs are currently used for targeted therapy in NPC patients, results are inconsistent or inconclusive and further large-scale clinical trials are still needed.^[18] Cetuximab is an EGFR monoclonal antibody approved for the treatment of advanced head and neck squamous cell carcinoma. A large-scale phase III clinical trial conducted by Bonner et al^[21] showed that addition of cetuximab significantly improved the OS and PFS of patients with head and neck squamous cell carcinoma concurrently treated with chemotherapy as compared to chemotherapy alone. However, there is still controversy regarding the use of cetuximab for advanced NPC as traditional high-dose cisplatin-based chemotherapy was not included for comparison, and the findings were inconsistent with those reported in several other clinical trials.^[22] Nimotuzumab is a humanized monoclonal antibody against EGFR, and several studies have shown that it has favorable short-term efficacy and good tolerance in NPC patients.^[23,24] However, large-scale clinical trials are required to evaluate its long-term efficacy. Gefitinib is a small molecule TKI of epidermal growth factor. In Hong Kong, it has been used in the treatment of recurrent or metastatic NPC in phase II clinical trials.^[25] However, no improvements were detected, and the specific efficacy of gefitinib needs to be further studied.^[25]

Vascular endothelial growth factor (VEGF) is involved in tumor angiogenesis and is closely related to the growth, invasion, metastasis, and prognosis of a variety of cancers. Currently, 5 antiangiogenic drugs are available for the treatment of advanced NPC, including bevacizumab and 4 small molecule VEGFR-TKIs (sorafenib, sunitinib, pazopanib, and vandetanib).^[26] However, although these targeted drugs, especially when combined with standard chemotherapy, are shown to delay disease progression, some with satisfactory safety, no effective drug for the targeted therapy of NPC is yet available and further study is needed.^[4,19] In a recent phase II trial comparing standard chemotherapy with standard chemotherapy plus bevacizumab that included 46 patients, bevacizumab combined with standard chemotherapy delayed disease progression with favorable safety.^[27] A phase III clinical trial is currently ongoing to investigate the efficacy of bevacizumab in the treatment of advanced NPC. Sorafenib is a multitarget drug with antitumor angiogenic activity and tyrosine kinase inhibition. In a phase II clinical trial, sorafenib showed good antiangiogenic effect with favorable tolerance in patients with metastatic NPC,^[28] and further investigation is ongoing. Sunitinib has dual antitumor activities that are similar to sorafenib. In patients with metastatic NPC who were nonresponsive to platinum-based chemotherapy^[29] or those previously treated with high dose radiation,^[30] severe hemorrhagic complications were observed. Thus, further analysis of the safety of sunitinib is warranted. Pazotinib exerts antitumor effects by inhibiting angiogenesis as well as enzymes related to tumor

growth. In a phase II clinical trial, pazotinib was used to treat Asian patients with advanced NPC, and results showed favorable safety and disease remission.^[31] Additional drugs targeting downstream molecules of the PI3K and mTOR-signaling pathways are being developed for targeted therapy of NPC. However, there is still no effective drug for the targeted therapy of NPC at present.

The apparent stabilization of advanced NPC and improvement in symptoms observed in the present case report was obtained with apatinib monotherapy alone after the patient had refused standard radiotherapy and chemotherapy. Given that the combination of antiangiogenic agents with radiotherapy may have synergistic effects,^[32] further studies combining apatinib with radiotherapy for advanced NPC are warranted. Moreover, enhanced targeted apatinib delivery via cyclic arginylglycylaspartic acid- and polyethylene glycol-modified liposomes may result in further antitumor activity with improved safety as shown through *in vivo* analysis.^[33]

With the exception of moderate hand-foot syndrome, the patient in the present case report did not experience any adverse events in response to the apatinib monotherapy. This favorable safety profile is similar to the findings of other previously published studies using this drug in patients with other cancer types with primary toxicities that included hypertension, hand-foot syndrome, proteinuria, and thrombocytopenia.^[6,10,13]

In conclusion, following apatinib treatment, the patient has survived with improved quality of life and few side effects. Although apatinib targets VEGFR-2, immunohistochemistry analysis showed that the tumor was negative for VEGFR-2. Thus, the effectiveness of apatinib might be ascribed to its multitarget activities, and other targets of apatinib should be further confirmed in future studies.

Author contributions

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