Addition of bevacizumab to systemic therapy for locally advanced and metastatic nasopharyngeal carcinoma

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Abstract. Radiotherapy is a vital treatment option for patients with nasopharyngeal carcinoma (NPC). Concurrent cisplatin-based radiochemotherapy with or without adjuvant chemotherapy had acquired good clinical effects with good local control rates. However, a number of patients present with metastasis following systemic regimens or initial diagnosis of locally advanced NPC, which cause difficulty for subsequent therapy. Therefore, there is an urgent requirement to discover novel targeted therapies. The present report describes one case of a patient with NPC and multiple metastases. The patient was treated with systemic therapy in combination with bevacizumab, palliative radiotherapy and chemotherapy following treatment with cetuximab and concurrent chemoradiotherapy in 2015. Following the addition of bevacizumab, metastases were reduced or disappeared after >2 months, and the duration of progression-free survival was 7 months. Bevacizumab is a monoclonal antibody that targets VEGF, and it is associated with angiogenesis, which causes the growth, invasion and progression of tumors. In previous studies, bevacizumab has been approved for the treatment of several types of malignant cancer and it has been able to effectively improve prognosis. In the present review, the effect of adding bevacizumab to systemic therapy for the treatment of NPC was analyzed, with a particular focus on advanced and metastatic diseases. A growing number of phase I/II clinical trials involving bevacizumab for NPC

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have been conducted with clinical outcomes showing improved rates of overall survival and progression-free survival as well as improvements in the quality of life of patients. However, severe or deadly toxicities can also result from combination treatment with bevacizumab. In the future, bevacizumab may become a common addition to systemic therapy for the treatment of locally advanced and metastatic NPC.

Introduction

NPC is endemic in Southern China, particularly in Guangdong and Guangxi (1). NPC originates from the epithelial lining of the nasopharynx, and it is classified into three histological types according to the World Health Organization (2-4). Type I NPC refers to keratinizing squamous cell carcinoma. Type II is non-keratinizing squamous cell carcinoma, and type III is undifferentiated squamous cell carcinoma (2-4). In general, types II and III are regarded together as undifferentiated carcinomas, where the incidence of metastasis is higher compared with type I NPC (3,5). In Guangdong province, the most common type of NPC is undifferentiated carcinoma, which is sensitive to radiation but is more prone to developing into distant metastasis compared with type I NPC (2,3,5). The undifferentiated type usually results in poor prognosis (6).

With the sensitivity of such disease to radiation, radiotherapy (RT) remains the mainstay treatment for patients with NPC (7,8). However, the majority of patients with NPC are initially diagnosed at late stages of the disease on the account of its complex anatomical location (1). These patients often miss the optimum treatment time because of therapy failure despite the development of RT methods, chemotherapy regimen, and targeted drugs, which results in relapse or distant metastasis (9). As reported, the 5-year local control rate of NPC ranges from 80 to 85, and ~30% of patients with NPC exhibit local recurrence and distant metastasis, which hinder successful treatment (10,11). In patients with metastasis, the 5-year overall survival (OS) rate ranges from 28 to 61%, and median OS (mOS) rate lasts ≥1-12 months (12). The cohort of patients with metastatic NPC presents poorer prognosis compared with those with non-metastatic diseases with OS of ~7-10 months (13).

The National Comprehensive Cancer Network guideline (version 1.2017) (14) recommends concurrent chemotherapy (with cisplatin preferably) and RT for locally advanced NPC and combined therapy for metastatic NPC (category 1 evidence). Systemic therapy for patients with locally advanced

NPC (stages III-IVb; American Joint Committee on Cancer manual; seventh edition) (15) is a concurrent chemoradiotherapy with or without cisplatin-based adjuvant chemotherapy with proven improved OS rates compared to patients treated with non-systemic therapies (7,8,16,17). Palliative chemotherapy remains the main strategy for patients with metastatic NPC (9). The addition of targeted therapy as a first-line treatment (or beyond) of locally advanced and metastatic NPC has a marked effects on outcomes, including progression-free survival (PFS) and OS rates (9). Along with RT and chemotherapy, treatment strategies involving anti-angiogenic therapy have been considered feasible in recent years (13,17).

Case report

The present authors treated a 21-year-old male with multiple metastatic undifferentiated non-keratinizing NPC (lymph nodes, bone, lung and pleura) based on nasopharyngeal biopsy pathology and positron emission tomography-computed tomography (PET-CT) with systemic therapy in combination with bevacizumab (7.5 mg/kg intravenously every 3 weeks), palliative RT of 30 Gy to the lumbosacral region and chemotherapy following treatment with cetuximab (initially at 400 mg/sqm, then 250 mg/sqm i.v., every 3 weeks, total 3 times) and concurrent chemoradiotherapy in the Affiliated Hospital of Guangdong Medical University (Zhanjiang, China) on May 21, 2015. The patient had a history of chronic hepatitis B for 3 years without any prior therapies, and a history of smoking and alcohol intake for 10 years. There were no similar cases in his family. Following the addition of bevacizumab, this patient experienced relief when metastasis was reduced or disappeared according to positron emission tomography-computed tomography (PET-CT) after >2 months (Figs. 1-6). The duration of PFS was 7 months, and the patient succumbed to disease in January 2016 as continuous treatment was refused due to economic factors. Nevertheless, the present case still provided strong evidence for the ability of bevacizumab to relieve cisplatin-induced resistance in combination therapy.

The rapid growth of tumors causes a lack of oxygen. Hypoxia-inducible factor (HIF)-1 is a transcription factor, and there are multiple isoforms, including HIF-1α and HIF-1β. HIF-1 is activated to regulate hypoxia-adaptive responses and activates downstream vascular endothelial growth factor (VEGF) genes, which play pivotal roles in a series of tumor-associated biological activities (Fig. 7) (1,18-23).

VEGF was initially discovered as a tumor-secreted protein (24) and can be detected in serum and tumor specimens (25). VEGF is located at chromosome 6p12, and it comprises a coding region with eight exons and seven introns (1). The VEGF gene family includes VEGF-A, -B, -C, -D and -E (13,26-28). Among these factors, VEGF-A is considered the most important in regulating tumor angiogenesis. There are three types of VEGF receptor (VEGFR) found on the cell surface: VEGFR-1, -2, and -3 (13). In particular, VEGF-A binds with VEGFR-1 and VEGFR-2, which leads to signal transduction (28,29). VEGF-C and -D regulate lymphatic vessel endothelium and promote lymphangiogenesis and invasion of tumor cells in patients with NPC via binding with VEGFR-3 (30).

VEGF is a tumor-induced factor that contributes to angiogenesis, tumorigenesis and metastasis (1,24,25,31-35). VEGF
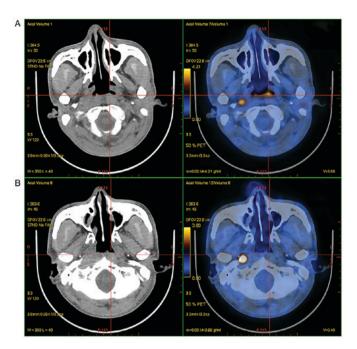

Figure 1. ^{18}F-FDG PET-CT scans of the whole body of the patient showing reduction in the site of an enlarged lymph node. (A) The PET-CT scan was taken in August 2015. A reduction in the enlarged lymph node (size, 1.0x1.1 cm) in the right posterior oropharynx with lower hypermetabolism is indicated compared with the scan taken in May 2015. SUVmax, 3.9. (B) The PET-CT scan was taken in May 2015. An enlarged lymph node (size, 1.0x1.3 cm) was detected in the right posterior oropharynx with hypermetabolism. SUVmax, 6.8. PET-CT, positron emission tomography-computed tomography; SUVmax, maximum standardized uptake value.

expression is associated with poor prognosis in patients with NPC (36). VEGF is expressed in head and neck cancer cells and in 67% of tumors from NPC biopsy specimens (11,12,31,37,38). The association between VEGF and angiogenesis has been reported in breast cancer, colorectal cancer and head and neck squamous cell carcinoma (HNSCC) (7,24). In one study, patients with decreased VEGF expression (77.8%) became disease-free, whereas patients with increased VEGF expression (66.7%) exhibited persistent or early relapse (25). The overexpression of VEGF increases the resistance of tumor cells to chemotherapy or RT and regulates the tumor microenvironment (1,2). One study has regarded high levels of VEGF expression to present difficulties for anti-epidermal growth factor receptor (EGFR) therapy (39). A potential mechanism for resistance is that VEGF protects endothelial cells from radiation and cytotoxic drugs and increases resistance of tumors to RT, chemotherapy and anti-EGFR therapy (40-42).

The concept of blocking angiogenesis, which may be a potential strategy for cancer treatment, was initially raised in 1971 (32). A growing number of studies on angiogenesis inhibitors in NPC were conducted since the concept was first raised (43). VEGF inhibitors decrease the density of blood vessels in tumors, which decrease the ability of tumors to meet its metabolic needs for growth and progression (26,28,44). This observation is the foremost mechanism of anti-VEGF therapy.

Vascular normalization window, when the function, structure and microenvironment of tumor blood vessels become normalized temporarily so that anticancer drugs can easily infiltrate into tumor tissue, is a typical factor for cancer radiosensitivity, implying that systemic therapy comprising anti-angiogenic
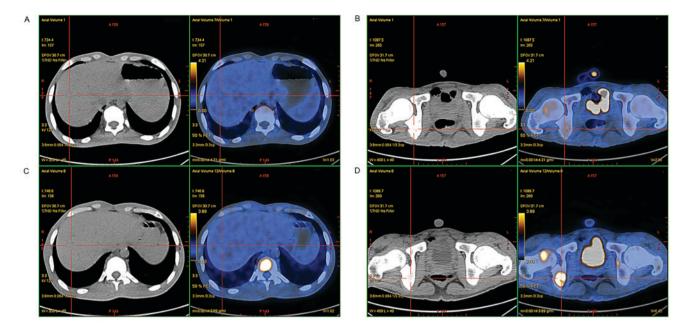
Figure 2. ^{18}F-FDG PET-CT scans of the whole body of the patient showing reducing in lymph node metastasis. (A) The PET-CT scans were taken in August 2015. A marked reduction in lymph node metastasis was detected in right neck with lower hypermetabolism compared with the scan taken in May 2015. SUVmax, 4.0. (B) The PET-CT scans were taken in August 2015. A marked reduction in lymph node metastasis was detected in left neck with lower hypermetabolism compared with the scan taken in May 2015. SUVmax, 4.0. (C) The PET-CT scans were taken in May 2015. Multiple metastatic lymph nodes were detected in right neck with hypermetabolism. SUVmax, 8.0. (D) The PET-CT scans were taken in May 2015. Multiple metastatic lymph nodes were detected in left neck with hypermetabolism. SUVmax, 8.0. PET-CT, positron emission tomography-computed tomography; SUVmax, maximum standardized uptake value.
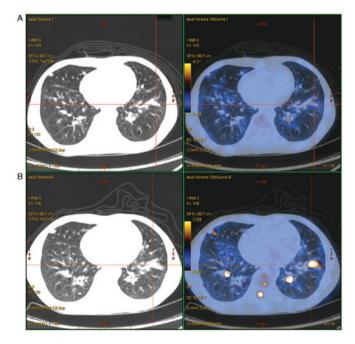

Figure 3. ^{18}F-FDG PET-CT scans of the whole body of the patient showing reduction of multiple nodular shadows in the left lung. (A) The PET-CT scan was taken in August 2015. Reduction of multiple nodular shadows of different sizes (maximum size, 0.5x0.8 cm) in the left lung with lower hypermetabolism was detected. SUVmax, 1.6. (B) The PET-CT scan was taken in May 2015. Multiple nodular shadows of different sizes (maximum size, 1.4x1.6 cm) with hypermetabolism were detected in the left lung. SUVmax, 5.6. PET-CT, positron emission tomography-computed tomography; SUVmax, maximum standardized uptake value.

therapy and radiation is not just a simple combination of the two therapies (26). Anti-angiogenic therapy increases radiation response in xenograft human models of NPC (1).

Bevacizumab (Avastin) is a recombinant humanized IgG1 monoclonal antibody that targets VEGF (Fig. 8) (31,32,45). In previous studies, bevacizumab has been demonstrated to have a definite clinical effect on inhibiting metastatic colorectal cancer, non-small-cell lung cancer, kidney cancer, gynecologic tumors and breast cancer (31,46). Bevacizumab therapy has contributed significantly to the outcomes of patients with malignant cancer, particularly those with systemic metastasis. To date, only cetuximab, an EGFR antibody, has been demonstrated to be effective for the treatment of locally advanced and metastatic NPC (42). However, the incidence of local recurrence and distant metastatic NPC remain at extremely high levels (41,43). Therefore, the development of novel targeted therapies is urgently required. Several studies have highlighted the anti-tumor effects of bevacizumab on HNSCC tumor xenografts in mice (6,44,45,47). Bevacizumab has no direct anti-tumor effect on NPC CNE1 cells *in vitro*, and this is potentially due to the lack of vascular endothelial cell receptors (12,18). Treatment with a combination of bevacizumab and paclitaxel exerts greater inhibitory effects compared with employing either agent alone. The use of the combination of bevacizumab and paclitaxel is able to prevent the formation of new blood vessels and trigger apoptosis in cultured tumor cells (31). Additionally, the use of anti-VEGF may increase the anti-tumor effect of RT and chemotherapy drugs potentially via the vascular normalization mechanism and the augmentation of endothelial cell injury (6,31,47). He *et al* (12) published a case in 2016 on a patient with stage IV NPC who was treated with a regimen of bevacizumab, paclitaxel, liposome and cisplatin. This patient achieved a stabilized condition 2 months following the addition of bevacizumab. The duration of PFS of the patient reached 7 months. Li *et al* (48) proposed that the combination of bevacizumab, cisplatin and TomoTherapy (TOMO) can result in good clinical effects, with 80% complete response and 40%
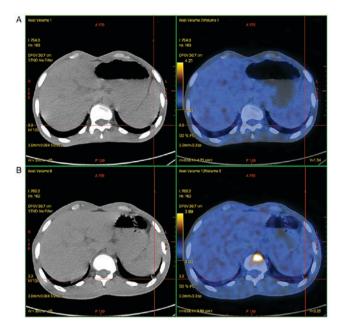
Figure 4. ^{18}F-FDG PET-CT scans of the whole body of the patient showing reduction of multiple nodular shadows in the left pleura. (A) The PET-CT scan was taken in August 2015. Reduction of multiple nodular shadows in the left pleura with lower hypermetabolism was detected. (B) The PET-CT scan was taken in May 2015. Multiple nodular shadows of different sizes with hypermetabolism were detected in the left pleura. PET-CT, positron emission tomography-computed tomography; SUVmax, maximum standardized uptake value.

Figure 5. ^{18}F-FDG PET-CT scans of the whole body of the patient showing the disappearance of multiple enlarged lymph nodes in the mediastinum. (A) The PET-CT scan was taken in August 2015. The disappearance of multiple enlarged lymph nodes in the mediastinum with lower hypermetabolism was detected. SUVmax, 3.7. (B) The PET-CT scan was taken in May 2015. Multiple enlarged lymph nodes (maximum size, 2.9x4.3 cm) in the mediastinum with hypermetabolism were detected. SUVmax, 8.4. PET-CT, positron emission tomography-computed tomography; SUVmax, maximum standardized uptake value.

partial response with low toxicity. The study by Li *et al* (48) was followed-up with 30 patients with stage III-IV NPC. The patients received a systemic therapy involving a combination of bevacizumab (5 mg/kg), cisplatin (80 kg/m^2) and RT (67. 5 Gy; helical TOMO) (48). This study provides basis for in-depth research on the use of anti-VEGF treatment and further verifies the curative effect of the addition of bevacizumab to therapy.
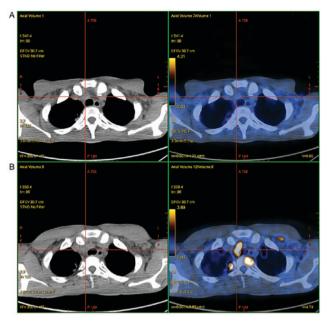
With regards to locally advanced and metastatic NPC, many clinical trials were carried out to test the efficacy and safety of bevacizumab. These trials offer theory of proof for clinicians (Table I). A phase II multi-institutional trial (RTOG 0615) showed that addition of bevacizumab to systemic chemoradiotherapy for patients with stage IIB-IVB NPC is feasible and may
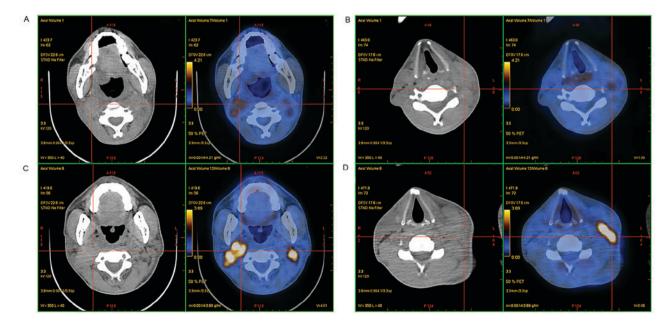

Figure 6. ^{18}F-FDG PET-CT scans of the whole body of the patient showing reduction of multiple bones metastases in the thoracic vertebrae and the right ischium. The PET-CT scans were taken in August 2015. A reduction in multiple bone metastases in the (A) thoracic vertebrae and the (B) right ischium was detected. The PET-CT scans were taken in May 2015. Multiple bone metastases in the (C) thoracic vertebrae and the (D) right ischium were detected. PET-CT, positron emission tomography-computed tomography; SUVmax, maximum standardized uptake value.

Table I. Details of clinical trials with combination therapy involving bevacizumab.

Treatment type (in addition to bevacizumab)	Disease setting	Phase	Year	Target	Mechanism of action	Results	(Refs.)
Erlotinib	Recurrent/metastatic (first or second-line)	I/II	2009	Anti-EGFR and anti-VEGF	Cytotoxic	RR, 15%; mPFS, 4.1 months; mOS, 7.1 months	(39)
Chemotherapy and RT	Newly diagnosed locally advanced cancer with poor-prognosis	I	2008	Anti-VEGF	Cytotoxic and radiation	mOS, 10.7 months	(51)
Erlotinib and concurrent chemotherapy/RT	Locally advanced (first-line)	II	2009	Anti-EGFR and anti-VEGF	Cytotoxic and radiation	ORR, 77%. 18-months PFS 85%, 18-months OS, 87%	(52)
Cisplatin and IMRT	Locally advanced (first-line)	II	2009	Anti-VEGF	Cytotoxic and radiation	Locoregional control rate, 100%; estimated 1-year PFS 83%; estimated 1-year OS, 88%	(53)
Cisplatin and IMRT	Locally advanced (first-line)	II	2012	Anti-VEGF	Cytotoxic and radiation	2-year PFS, 75.9%; 2-year OS, 88%	(50)

EGFR, epidermal growth factor receptor; RR, response rate; IMRT, intensity-modulated relation therapy; mPFS, median progression-free survival; mOS, median overall survival; ORR, overall response rate; RT, radiotherapy; VEGF, vascular endothelial growth factor.
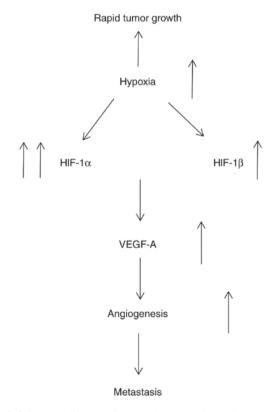

Figure 7. Schematic diagram of the development of nasopharyngeal carcinoma metastasis via VEGF. HIF, hypoxia-inducible factor; VEGF, vascular endothelial growth factor.

Figure 8. Signaling pathway that is deregulated by bevacizumab in nasopharyngeal carcinoma. VEGFR, vascular endothelial growth factor receptor.

function in blocking invasion of tumor cells (49). The combination of bevacizumab and erlotinib improves efficacy with an observed response rate of 1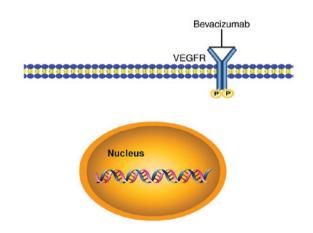5%, whereas severe or late side effects have not been observed in another phase II trial (39). A phase I research on bevacizumab, fluorouracil, hydroxyurea and radiation in patients with recurrent NPC, achieved promising mOS rate of 10.7 months (50). Pfister et al (51) treated patients with locally advanced HNSCC using protocol of bevacizumab and cisplatin and intensity-modulated radiation therapy (IMRT), which yielded 100% locoregional control rate, 83% 1-year PFS rate, and 88% 1-year OS rate in 2009. Similarly, in 2012, Fury et al (52) also conducted a phase II study on patients with stage III-IV HNSCC and treated them with the same treatment as those of Pfister et al (51); this study yielded 75.9% 2-year PFS rate and 88% 2-year OS rate. Meluch et al (53) conducted a trial on patients with locally advanced HNSCC and treated with bevacizumab, erlotinib, chemotherapy, and RT; their study obtained an objective response rate of 77%, 18-month PFS rate

of 85%, and 18-month OS rate of 87% (53). Some phase III trials have surveyed recurrent or metastatic HNSCC (E1305) (54). Phase I/II studies are common, whereas phase III studies are rarely conducted. More tests are urgently needed to confirm feasibility of combination of bevacizumab and chemotherapy or RT. Addition of bevacizumab to RT may be a promising strategy and may restrain poor preclinical outcomes.

The usual side effects of bevacizumab include hypertension, bleeding, gastrointestinal perforation, cardiotoxicity, and thromboembolic events (32,55). In the past, patients treated with anti-angiogenetic drugs surrendered early due to severe and lethal side effects. However, with the development of drugs and clinical management, common side effects are now easily managed. The trials above recorded absences of grade 3 or grade 4 hemorrhage and late unexpected effects. A phase I study was conducted by Seiwert *et al* (50), who demonstrated that the safe dose of bevacizumab is 10 mg/kg every 2 weeks when added to fluorouracil and hydroxyurea-based chemoradiotherapy.

Targeted therapy is a novel strategy that has achieved remarkable progress in recent years. Various targeted drugs have been found and tested in clinical trials. However, few of them have been approved by the US Food and Drug Administration, which required further randomized trials. Gene mutation of the tumor is also a key point for sensitivity of targeted therapy (56). In the future, molecular targeted drugs should be more specific and feature a narrow spectrum with minimal toxicity in clinical use for suitable patients after strict selection (57).

In conclusion, bevacizumab is effective and safe when added to RT and chemotherapy for patients with locally advanced and metastatic NPC. Several phase I II clinical trials have shown promising results in terms of local control and survival rates. However, phase III trials are insufficient to change the therapeutic principle, rendering an urgent need for additional in-depth studies. In the future, bevacizumab may be a potential molecular target drug for locally advanced and metastatic NPC.

Acknowledgements

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

QLL designed the study; XXP and SAC collected the patient data; GLY, LJ and HJZ read and analyzed the literature; HJZ wrote the manuscript; HJZ and QLL critically revised the manuscript. The final version of the manuscript was read and approved by all authors.

Ethics approval and consent to participate

The present study was has been approved by the Affiliated Hospital of Guangdong Medical University Ethics Committee (Zhanjiang, China), and informed consent was obtained from the participating patient.

Consent for publication

Written informed consent for the publication of the clinical details and images was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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