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RESEARCH ARTICLE

A Pilot Study of Anlotinib as a Combination Treatment in Advanced Nasopharyngeal Carcinoma

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Abstract: ***Aims*:** To investigate the short-term objective response and treatment toxicity of anlotinib as a combination treatment in patients with Recurrent or Metastatic Nasopharyngeal Carcinoma (RM-NPC).

***Methods*:** Patients with RM-NPC who received anlotinib as a combination treatment between March 2021 and July 2022 were retrospectively analyzed.The efficacy and safety of anlotinib as a combination treatment were analyzed.

***Results*:** A total of 17 patients with RM-NPC were included in this study. Of these patients, 2 (11.8%) had local recurrence, 4 (23.5%) had cervical lymph node recurrence, and 11 (64.9%) had distant failure. The most common metastatic site was the liver (47.1%), followed by the lung (23.5%) and bone (23.5%). Anlotinib was given as first-line treatment in 3 patients (17.6%), second lines treatment in 7 patients (41.2%), and third to six-lines treatment in 7 patients (41.2%). All patients received anlotinib combined with chemotherapy and/or immunotherapy. One patient achieved a complete response (5.9%), 7 patients had a partial response (41.2%), 5 patients had stable disease (29.4%), and 4 patients had progressive disease (23.5%). The overall disease control rate and the overall response rate were 76.5% and 47.1%, respectively. The median progression-free survival was 8.1 months, and the median overall survival was not reached. The incidence of grade 3 adverse events was 30%. No unexpected side effects or treatment-related death were observed.

***Conclusion*:** Anlotinib, as a combination treatment, has a promising antitumor activity and a manageable safety profile in patients with RM-NPC. Our results add to the growing evidence that supports the benefits of combining antiangiogenic drugs in RM-NPC. Randomized controlled clinical trials investigating the evaluation of anlotinib are warranted.

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1. INTRODUCTION

Nasopharyngeal Carcinoma (NPC) is a common head and neck malignancy with obvious ethnic susceptibility, regional aggregation, and familial tendency [1]. Although there are rigorous standards of radiation and chemotherapy of NPC, approximately 20-30% of the patients still have disease progression after treatment [2-4]. Among the patients with disease recurrence, the combination of immunotherapy plus gemcitabine and cisplatin regime showed survival benefits compared to those treated with chemotherapy alone [5, 6]. However, there were still have at least 25% of the patients were not completed the palliative treatment due to treatment- related toxicity, and the median Progression-free Survival (PFS) was less than 7 months in patients with disease recurrence after palliative treatment [7-10]. Hence, there is an urgent need to investigate novel treatments that are effective and well-tolerated for this population.

Chemotherapy and radiotherapy are traditional methods adopted to treat NPC [11, 12]. In recent years, several treatment strategies, including immunotherapy, virotherapy, and gene therapy, have been explored in the cancer treatment of patients [13-16]. Several previous studies also have revealed that angiogenesis is an important part of the treatment strategy for malignant solid tumours, especially for patients with recurrence and metastasis gastric or non-small-cell lung cancer [17-19]. By broadly targeting vascular endothelial growth factor receptors (especially type 2 and 3), Platelet-Derived Growth Factor b (PDGFRb), and stem cell factor receptor (c-Kit), anlotinib has shown significant survival benefits in lung, gastric, and esophageal cancer [18-20]. Although there were several phase II clinical trials showed durable disease control in metastatic NPC using antiangiogenic agents such as axitinib, pazopanib, and apatinib [10, 21, 22],

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limited studies investigated the role of anlotinib in Recurrent or Metastatic NPC (RM-NPC). In light of this, this pilot study aimed to investigate the short-term objective response and treatment toxicity of anlotinib as a combination treatment in RM-NPC.

2. MATERIALS AND METHODS

2.1. Patient Selection

In March 2021, we initially used anlotinib in patients with RM-NPC in our institution. Patients who met the following criteria between March 2021 to July 2022 were retrospectively included: 1) pathologically confirmed NPC, 2) had tumor locoregionally recurrence and/or distant metastasis, 3) had progressive disease after palliative treatment or intolerable to chemotherapy, 4) received anlotinib in combined with other therapies. All patients signed informed consent before anlotinib treatment. This study was approved by the Institutional Review Board of the First Affiliated Hospital of Xiamen University (approval number: 3502Z20-224ZD1005).

2.2. Measures

The following patient and disease characteristics were included in this study: age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, histology, the sites of disease recurrence, previous therapeutic history, the combination of other therapies, the date for initial treatment of anlotinib, the reason for treatment discontinuation, the toxicity of anlotinib, time to second disease progression, and date of death if available.

2.3. Treatment

In this study, patients received anlotinib combined with other therapies until disease progression or unacceptable toxicity. Anlotinib was administered at a dose of 12 mg daily on d1-d14 every 3 weeks [23]. Grade 3 Adverse Event (AE) required reversion to grade 2 before continuation of anlotinib treatment, and the dose of anlotinib was reduced to 12 mg every 2 or 3 days. The chemotherapy regimen included gemcitabine, docetaxel, albumin-bound paclitaxel, oral tegafur, or capecitabine among these patients. The immunotherapy regimen included pembrolizumab, camrelizumab, toripalimab, and tislelizumab.

2.4. Evaluation of Treatment Response and Treatment-related Adverse Event

All patients received an imaging examination every two medication cycles to evaluate the clinical response to treatment. Treatment response was defined as response (CR), Partial Response (PR), Stable Disease (SD), and Progressive Disease (PD) using the RECIST criteria 1.1. The overall Response Rate (ORR) was defined as CR + PR. The Disease Control Rate (DCR) was defined as CR + PR + SD. AEs were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events 4.0 (NCI-CTCAE 4.0).

2.5. Statistical Analysis

The direct counting method was used to calculate the baseline data and AE data of the patients. PFS was defined as the time from initiation of anlotinib to disease progression or death. Overall Survival (OS) was defined as the time from anlotinib treatment to patient death or last follow-up. The Kaplan-Meier survival curve was used to analyze the survival rate. All statistical descriptive analyses were conducted by SPSS 26.0 software (SPSS Inc., Chicago, IL, USA).

3. RESULTS

3.1. Patient Baseline Characteristics and Treatment

A total of 17 patients were included. The median age at NPC diagnosis was 51 years (range, 30-80 years). Table **1** lists the baseline clinicopathological and treatment characteristics of the patients. Of these patients, 2 (11.8%) had local recurrence alone, 4 (23.5%) had cervical lymph node recurrence alone, and 11 (64.9%) had a distant failure with or without locoregional recurrence. 16 sites of distant metastasis were observed; the most common metastatic site was the liver (8/16, 47.1%), followed by the lung (4/16, 23.5%) and bone (4/16, 23.5%).

All patients received anlotinib combined with chemotherapy and/or immunotherapy. Anlotinib was given as first-line treatment in 3 patients (17.6%), second lines treatment in 7 patients (41.2%), and third to six-lines treatment in 7 patients (41.2%). There were 11 patients (64.7%) received anlotinib in combined chemotherapy, 3 patients (17.6%) received anlotinib combined with immunotherapy, and 3 patients (17.6%) received a combination of anlotinib, chemotherapy, and immunotherapy. Patients also received palliative radiotherapy if necessary.

The median time for anlotinib maintenance treatment was 6 months (range, 1-14 months), and the common dosage for anlotinib was 12 mg. Dose adjustment occurred in 3 patients whom inability to tolerate anlotinib and the prescription was modified to anlotinib 12 mg every 2 or 3 days.

3.2. Objective Response and Survival Data

The median follow-up was 9.4 months (range, 3.2-18.2 months). On September 5, 2022, all patients received a tumor response assessment. There were 1 (5.8%), 7 (41.2%), 5 (29.4%), and 4 (23.5%) patients who had CR, PR, SD, and PD, respectively (Table **2**). The DCR and ORR were 76.5% (13/17) and 47.1% (8/17), respectively. Fig. (**1**) shows the waterfall plot of the response to anlotinib. For the intent-to-treat population, the median PFS was 8.1 months (95% Confidence Interval (CI) 5.87-10.34). Three patients died of NPC, and the median OS was not reached (Fig. **2**). In those treated with anlotinib and chemotherapy (n=11), 1 (9.1%) patient achieved CR, 4 (36.4%) patients had PR, 3 (27.3%) patients had SD, and 3 (27.3%) patients had PD. The overall ORR and DCR were 45.5% (5/11) and 72.8% (8/11), respectively. In those treated with anlotinib and immunotherapy (n=3), 2 (66.7%) patients achieved PR, and 1 (33.3%) patient had SD. In those receiving anlotinib, chemotherapy, and immunotherapy (n=3), 1 (33.3%) patient achieved PR and 2 (66.7%) patients had SD (Table **2**).

Fig. (**3A**) describes the case of a patient with T2N3M0 NPC patient who experienced left neck lymph node recurrence 15 months after receiving induction chemotherapy and

Table 1. Patient baseline characteristics.

Characteristics	No. (n=17)	%
Age (Years)		
Median (range)	51 (30-80)	-
Gender		
Male	13	76.5
Female	4	23.5
ECOG		
0	11	64.7
1	6	35.3
Histology		
Non-keratinizing undifferentiated	12	70.6
Non-keratinizing differentiated	5	29.4
Keratinizing	0	0
Treatment Line [a]		
First line	3	17.6
Second line	7	41.2
Subsequent line	7	41.2
Treatment Scheme		
Anlotinib + chemotherapy	11	64.7
Anlotinib + immunotherapy	3	17.6
Anlotinib + chemotherapy + immunotherapy	3	17.6
Previous Radiotherapy		
Yes	14	82.4
No	3	17.6

Note: Data are presented as the median or n (%) unless otherwise stated.
Abbreviations: ECOG, Eastern Cooperative Oncology Group performance status.
[a]Patients diagnosed with recurrent or metastatic nasopharyngeal carcinoma received anlotinib as first/second or subsequent line treatment.

concurrent chemoradiotherapy (Fig. **3A1**). The patient received the combination of anlotinib and gemcitabine-cisplatin (GP) regimen. After 6 cycles of treatment, the treatment response assessment of this patient was PR (Fig. **3A2**), and liver metastasis occurred 10 months after maintenance treatment with anlotinib.

Fig. (**3B**) lists the case of a patient with T4N2M0 NPC patient who experienced pleural metastasis 8 months after receiving induction chemotherapy and concurrent chemoradiotherapy, and the pathological biopsy confirmed the metastasis was from NPC. After receiving 6 cycles of GP regimen palliative chemotherapy, the pleural metastatic lesions progressed 10 months later (Fig. **3B1**). The patient received second-line treatment with anlotinib and toripalimab (a monoclonal antibody against human programmed death-1). After 3 cycles of treatment, the treatment response assessment of this patient was CR (Fig. **3B2**), and axillary lymph node metastasis occurred 6 months after maintenance treatment with anlotinib and toripalimab.

3.3. Toxicity Assessment

10 patients developed at least one Treatment-related Adverse Event (TRAE) and most of the adverse events were grade 1-2 in severity (Table **3**). The incidence of grade 3 AEs was 30% (3/10). No unexpected side effects or treatment-related death were observed. The most common anlotinib-related AEs were hyperlipemia (n=6, 60%), oral mucositis (n=4, 40%), secondary hand-foot syndrome (n=2, 20%), hepatic dysfunction (n=2, 20%), hypertension (n=1, 10%), muscle pain/joint pain (n=1, 10%). Three patients ceased anlotinib due to grade 3 AEs (oral mucositis, muscle pain/joint pain, and diarrhea).

Table 2. The efficacy of anlotinib alone and in combination with other drugs.

Parameter	Best Response				ORR	DCR
	CR	PR	SD	PD		
Total	1	7	5	4	47.1% (8/17)	76.5% (13/17)
Combined Regimen						
Chemotherapy	1	4	3	3	45.5% (5/11)	72.7% (8/11)
Immunotherapy	0	2	1	0	66.7% (2/3)	100% (3/3)
Both	0	1	2	0	33.3% (1/3)	100% (3/3)

Abbreviations: CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease; ORR, Overall Response Rate; DCR, Disease Control Rate.

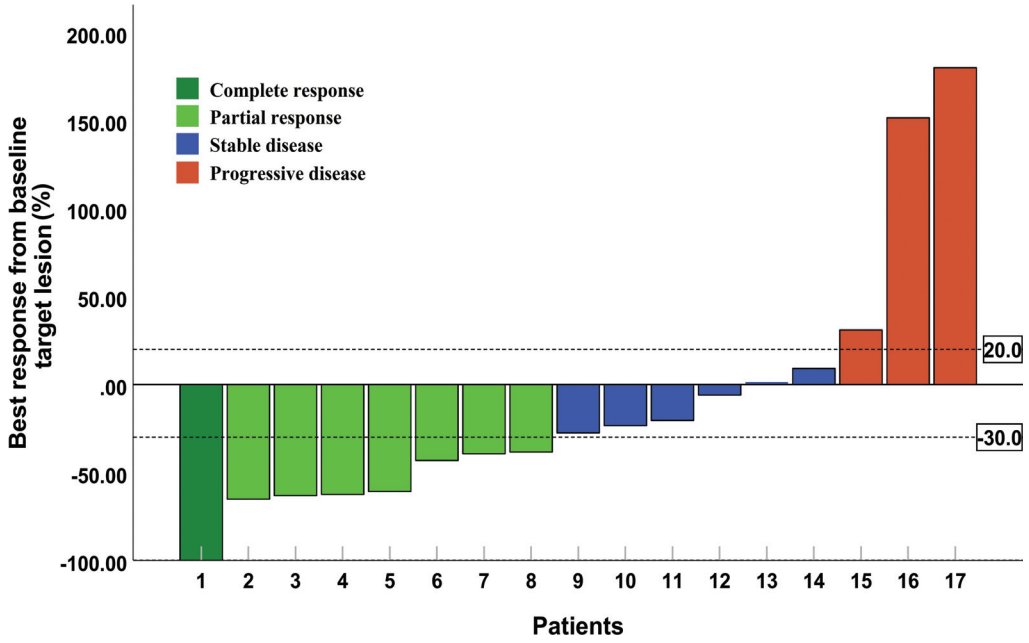

Fig. (1). Waterfall plot of the best response change. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

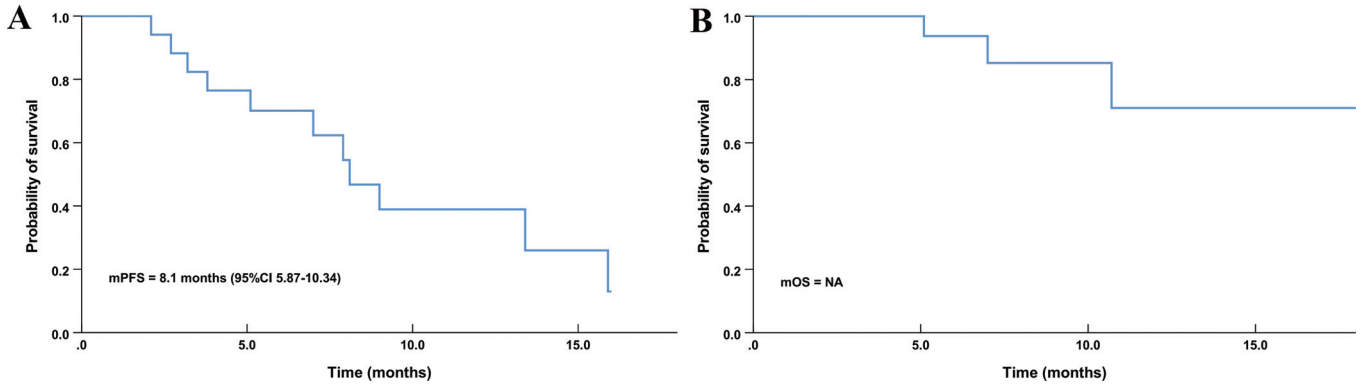

Fig. (2). (**A**) Kaplan-Meier curve of PFS and (**B**) OS in the general population. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

4. DISCUSSION

Although there were several clinical trials investigated the efficacy and safety of antiangiogenic agents in RM-NPC, limited studies assess the role of anlotinib in this population. This pilot study investigated the short-term objective response and treatment toxicity of anlotinib combined with other therapies in RM-NPC. We found a promising antitumor activity and a manageable safety profile using anlotinib in this population.

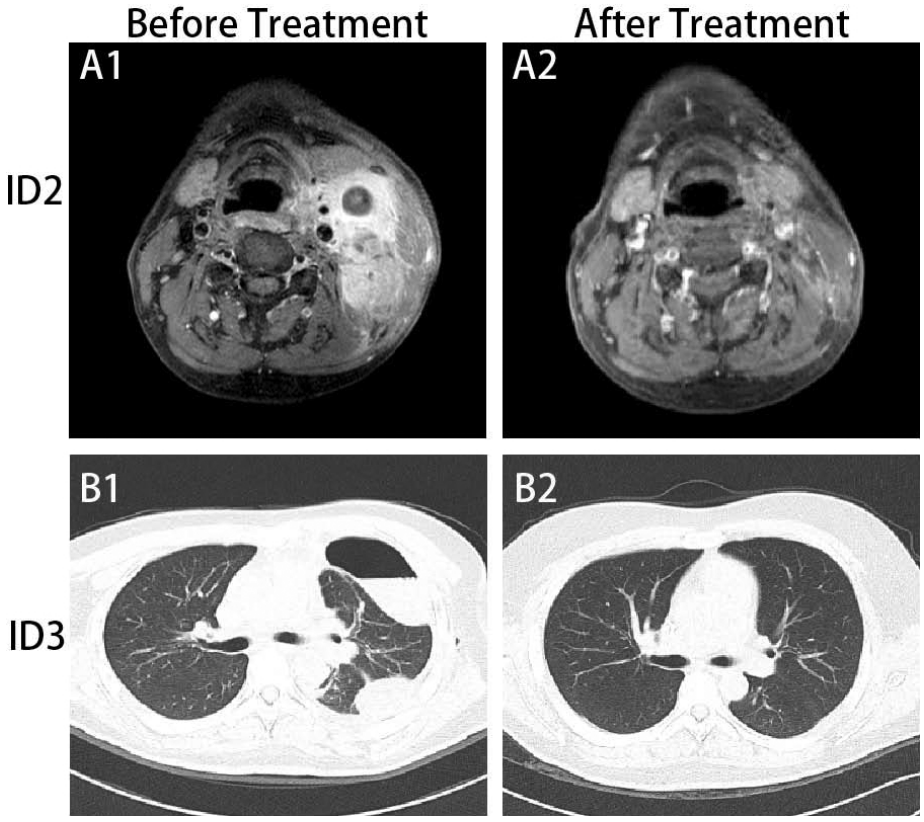

Fig. (3). Changes in (**A1-A2**) cervical metastatic lymph nodes and (**B1-B2**) pulmonary metastases in patient ID2 and ID3, respectively. Magnetic resonance images show the reduction of lymph nodes, and computed tomography images show recovery in pulmonary metastasis after anlotinib combined treatment. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Table 3. Major treatment-related adverse events (n=10).

Adverse Events	All Grades n (%)	≥ Grade 3 n (%)
Non-hematologic		
Oral mucositis	4 (40%)	1 (10%)
Hand-foot syndrome	2 (20%)	-
Diarrhea	1 (10%)	1 (10%)
Muscle pain/joint pain	1 (10%)	1 (10%)
Hypertension	1 (10%)	-
Hematologic		
Hyperlipemia	6 (60%)	-
Hepatic dysfunction	2 (20%)	-

Systemic chemotherapy combined with an immune checkpoint inhibitor is the preferred regimen for RM-NPC in the current treatment guidelines [24]. Although the combination of chemotherapy and immune checkpoint inhibitor has brought a median PFS of 11 months, a considerable number of patients will develop disease progression [5, 25]. Once the disease progresses, the ORR of less than 30% and the median PFS of less than 7 months in those treated with second-line treatment using immunotherapy or chemotherapy [7 ,9, 21, 22].

Having a comprehensive understanding of tumor biology and cancer genetics, including the immunological and molecular microenvironment, is crucial to explore new therapeutic strategies for treating NPC. Various biomarkers, such as those related to the immunological microenvironment, cancer genetics, and molecular biology, have paved the way for novel methods of treating NPC. In recent years, several preclinical studies have shown that antiangiogenic drugs could significantly inhibit tumor cell growth and metastasis by targeting Vascular Endothelial Growth Factor Receptor

(VEGFR) [26, 27]. Overexpression of VEGFR has been identified in 60-67% of NPC patients and has been associated with poor survival rates [28, 29]. The VEGFR pathway plays a critical role in angiogenesis, tumor growth, and metastasis, making it a potential therapeutic target of NPC [30, 31].

Furthermore, antiangiogenic therapy has been shown to synergize with chemotherapy in inhibiting NPC xenografts, leading to improved mouse survival rates [32]. Thus, the combination of antiangiogenic therapy and chemotherapy may effectively enhance the response to treatment. While the high expression of VEGFR in NPC cells and their anticancerous effects show promise, further investigation is necessary to determine the effect of antiangiogenic therapy in NPC patients. However, there is still insufficient evidence to determine the impact of antiangiogenic therapy on NPC patients.

Anlotinib is a multi-target TKI, which can inhibit VEGFR, PDGFR, FGFR, c-Kit, and other pathways and ultimately inhibit angiogenesis [23, 33, 34]. Several studies have demonstrated the efficacy of anlotinib in advanced solid cancer, including colon adenocarcinoma and non-small cell lung cancer [19, 23]. A phase III trial showed that anlotinib as a third-line treatment could prolong PFS by 4.0 months and OS by 3.3 months in patients with advanced non-small cell lung cancer [35]. In two small samples of phase II studies, apatinib monotherapy in late-line advanced NPC could bring 31.7% and 36.4% of ORR, respectively [22, 36]. Axitinib, another anti-angiogenesis, showed a 19% ORR, 5 months of PFS, and 10.4 months of OS in advanced NPC [10].

Anlotinib has been reported to have stronger antiangiogenic activity than other drugs, such as sorafenib, sunitinib, and nintedanib [33]. In addition, its broad target range may help overcome drug resistance induced by previous chemotherapy or targeted therapies [37]. Anlotinib has also been found to ameliorate the immunological microenvironment by downregulating PD-L1 expression on vascular endothelial cells, which helps inhibit tumor growth [38]. When combined with a PD-1 checkpoint inhibitor, anlotinib has been shown to counteract the immunosuppression caused by the upregulation of PD-L1 after monotherapy, leading to extended periods of vascular normalization and ultimately inducing tumor regression [39]. However, there are limited studies on anlotinib for NPC. In 2020 ESMO, an interim analysis of a phase II study of anlotinib for recurrent and metastatic NPC, reported that 17.6% (3/17) of ORR, median PFS was 3.3 months with a median follow-up time of 5.4 months [40]. Compared with monotherapy anlotinib maintenance therapy, combining chemotherapy or immunotherapy is an effective approach for antiangiogenic therapy. In this study, we observed that the ORR and DCR in our cohort were 47.1% and 76.5%, respectively, which was significantly higher than in the previous study with monotherapy anlotinib maintenance therapy [40]. However, due to the short follow-up time and small sample size enrolled, the optimal combination treatment strategies still needed to be further explored.

Similar to previous research [41, 42], the most common adverse events using anlotinib combined therapy were hyperlipemia (60%), oral mucositis (40%), secondary hand-foot syndrome (20%) and hepatic dysfunction (20%, mainly up-regulation of ALT/AST). The most intolerable adverse events by patients were grade 3 oral ulcers, muscle/joint pain, and diarrhea. All of these resulted in dose reduction or treatment interruption. Compared with existing studies of antiangiogenic agents, we observed few severe bleeding events in these 17 enrolled patients. This may be related to the fact that we adjusted the medication frequency of anlotinib from 12 mg once d1-14 to once every 2 or 3 days, according to the patient's tolerance. Nevertheless, there are no controlled studies on the dosage reduction mode, whether a single dose reduction or a change in oral frequency.

Several limitations should be acknowledged in this study. First, the retrospective nature of the study has inherent risks of bias. Second, the combination of anlotinib with other treatment strategies in our study makes it difficult to evaluate the efficacy of anlotinib in this population accurately. Finally, our study was also limited to a short follow-up time and a small sample size enrolled.

CONCLUSION

In conclusion, our study suggests that anlotinib as a combination treatment has promising antitumor activity and tolerable toxicity in patients with RM-NPC. Our results add to the growing evidence that supports the benefits of combining antiangiogenic drugs in RM-NPC. Given these findings, prospective studies are required to explore the effect of anlotinib in patients with RM-NPC.

AUTHORS' CONTRIBUTIONS

Rui Zhou and Ping Zhou collected the clinical and pathological data. Yi-Feng Yu and Ping Zhou analyzed and organized the data and wrote the manuscript. Rui Zhou assisted in revising the manuscript. Qin Lin and San-Gang Wu revised the manuscript, approved to publication of the manuscript, and agreed to be accountable for all aspects of the work.

LIST OF ABBREVIATIONS

AE	=	Adverse Event
CI	=	Confidence Interval
CR	=	Complete Response
DCR	=	Disease Control Rate
ECOG	=	Eastern Cooperative Oncology Group
GP	=	Gemcitabine Cisplatin
NCI-CTCAE 4.0	=	National Cancer Institute Common Terminology Criteria for Adverse Events 4.0
NPC	=	Nasopharyngeal Carcinoma
ORR	=	Overall Response Rate
OS	=	Overall Survival
PD	=	Progressive Disease
PDGFRb	=	Platelet Derived Growth Factor b

PFS	=	Progression-free Survival
PR	=	Partial Response
RM-NPC	=	Recurrent or Metastatic Nasopharyngeal Carcinoma
SD	=	Stable Disease
TRAE	=	Treatment-related Adverse Event
VEGFR	=	Vascular Endothelial Growth Factor Receptor

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xiamen University (Approval number: 3502Z20224ZD1005).

HUMAN AND ANIMAL RIGHTS

This research was conducted on humans in accordance with the Helsinki Declaration of 1975, as revised in 2013 [http://ethics.iit.edu/ecodes/node/3931].

CONSENT FOR PUBLICATION

Informed consent was obtained from all patients.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article are available within the article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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