



# Apatinib in treating patients with recurrent or metastatic nasopharyngeal carcinoma who had failed prior platinum-based chemotherapy

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**Background:** Platinum-based chemotherapy is the standard first-line treatment for recurrent/metastatic nasopharyngeal carcinoma (NPC); however, there is no standard regimen for those who failed first-line treatment. This study aimed to evaluate the efficacy and safety of apatinib in treating patients with recurrent/metastatic NPC who failed prior platinum-based chemotherapy.

**Methods:** Patients aged 18–65 years with recurrent/metastatic NPC were treated with apatinib at an initial dose of 500 mg once daily and continued until disease progression, patient withdrawal, or unacceptable toxic effects. The primary endpoints were clinical benefit rate (CBR) and toxicity. Secondary endpoints included progression-free survival (PFS) and overall survival (OS).

**Results:** Nineteen patients were enrolled in this study. At the final follow-up, the CBR was 52.6% (95% CI: 29.8–76.2%) in the intention-to-treat population. The median PFS and OS were 3.7 (95% CI: 0.6–6.8) months and 12.9 (95% CI: 9.3–16.5) months, respectively. The most common grade 3–4 adverse events (AEs) were hand-foot syndrome [3 (15.8%)], neutropenia [2 (10.5%)], proteinuria [2 (10.5%)], oral mucosal pain [2 (10.5%)], hypertension [1 (5.3%)], hyponatremia [1 (5.3%)], artery dissection [1 (5.3%)], and nasopharyngeal hemorrhage [1 (5.3%)]. A serious AEs was reported in one patient who died of nasopharyngeal hemorrhage. Treatment with apatinib did not significantly influence patient-reported quality-of-life, except for nausea/vomiting and pain ( $P < 0.05$ ).

**Conclusions:** Apatinib achieved modest disease control with acceptable toxicity in recurrent/metastatic NPC patients pretreated with platinum-based chemotherapy.

**Keywords:** Apatinib; nasopharyngeal carcinoma (NPC); recurrent or metastatic; platinum-based chemotherapy; toxicity

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## Introduction

Nasopharyngeal carcinoma (NPC) is a common type of malignancy in south China and southeastern Asia (1,2). The widespread application of intensity-modulated radiotherapy (IMRT) and an optimized chemotherapy regimen (induction, concurrent and adjuvant) have improved the 5-year overall survival (OS) rates for NPC to about 85% (3). However, about 30% of NPC patients have recurrent or metastatic disease despite undergoing radical chemoradiotherapy (4).

Platinum-based chemotherapy is commonly used as a standard first-line treatment for NPC. A recently published phase III clinical study showed gemcitabine plus cisplatin exhibits preferable anti-tumor activity than fluorouracil plus cisplatin in recurrent or metastatic NPC [median progression-free survival (PFS) of 7.0 versus 5.6 months, respectively] (5). However, the optimal therapeutic regimen for those who failed this first-line chemotherapy have not yet been established.

Several multi-kinase tyrosine kinase inhibitors (e.g., sorafenib, sunitinib, pazopanib, and axitinib) have already shown a favorable clinical benefit in recurrent/metastatic NPC, with a median PFS of 3.2–7.2 months (6–9). However, a phase II study detected a high incidence of hemorrhagic complications with sunitinib in recurrent/metastatic NPC (9). Therefore, we require more effective and safe treatment regimens for patients with metastatic/recurrent NPC.

The vascular endothelial growth factor receptor (VEGFR) family of proteins consists of VEGFR-1, VEGFR-2, and VEGFR-3. Among them, VEGFR-2 is the principal mediator of VEGF-induced angiogenic signaling. Apatinib is a highly-selective inhibitor of VEGFR-2. Using an *in vivo* murine model of NPC, Peng *et al.* confirmed that the administration of apatinib inhibited tumor growth, reduced microvascular density, and facilitated tumor apoptosis in tumor-bearing mice (10). However, the clinical efficacy of apatinib in NPC patients remains unclear.

This phase II clinical study aimed to evaluate the efficacy and safety of apatinib in treating patients with recurrent/metastatic NPC who failed prior platinum-based chemotherapy. We also evaluated the quality-of-life (QOL) after administration of apatinib in this patient cohort. We present the following article in accordance with the TREND reporting checklist (available at <http://dx.doi.org/10.21037/tcr-20-1773>).

## Methods

### Study design

This was a prospective, phase II clinical trial conducted at the Zhejiang Cancer Hospital. The study protocol was approved by the ethics committee of the Zhejiang Cancer Hospital (NO: IRB-2017-126) and was performed in accordance with the Declaration of Helsinki (as revised in 2013) and Good Clinical Practice guidelines as defined by the International Conference on Harmonization. All patients provided written informed consent before taking part.

The primary endpoints were clinical benefit rate (CBR) and toxicity. CBR is defined as the percentage of patients achieving complete response, partial response, or stable disease according to the Response Evaluation Criteria In Solid Tumors (RECIST 1.1) criteria. Secondary endpoints included PFS and OS. The PFS was defined as time from the initiation of treatment to the date of disease progression or death from any causes, whichever came first; and OS was defined as time from the initiation of treatment to the time of death. We used Simon's two-stage design, and analyzed the efficacy and toxicity in the intention-to-treat population (11). This study is registered with ClinicalTrials.gov, number NCT03213587.

### Patient selection

Patients enrolled in this study were histologically or cytologically confirmed cases of recurrent or metastatic NPC who had failed at least one prior line of platinum-based chemotherapy for recurrent or metastatic disease. Other eligibility criteria were: at least one lesion accurately measured according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1); an Eastern Cooperative Oncology Group performance status (ECOG score) of 0 to 2; aged 18 to 65 years; adequate organ function (i.e., white blood cell count of  $\geq 4.0 \times 10^9/L$ ; absolute neutrophil count of  $\geq 1.5 \times 10^9/L$ ; hemoglobin concentrations of  $\geq 90$  g/L; platelet cell count of  $\geq 100 \times 10^9/L$ ; aspartate transaminase and alanine transaminase of  $< 2.5 \times$  the upper limit of the normal (ULN); if liver metastases, serum transaminase  $< 5 \times$  the ULN; and creatinine clearance rate of  $\geq 60$  mL/min); an estimated life expectancy of  $\geq 3$  months; written informed consent; and amenable for regular follow-up.

Patients with any of the following conditions were

excluded: prior therapy with a tyrosine kinase inhibitor targeting VEGFR or platelet-derived growth factor receptor (PDGFR); any factors that influence the usage of oral administration; known spinal cord compression or diseases of the brain or pia mater by CT/MRI screening; history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 1 month of treatment, any history of cerebrovascular accident and artery or venous thromboembolic events within the last 6 months; any history of myocardial infarction, unstable angina pectoris, cardiac angioplasty or stent implantation within the last 3 months; blood coagulation abnormal with hemorrhagic tendency or thrombolysis or anticoagulation therapy. Patients with a preexisting serious accompanying disease that may put them at risk or influence their compliance, and those with secondary malignancies (except cured basal cell carcinoma of the skin and carcinoma in-situ of the uterine cervix) were excluded.

#### *Study treatment and assessment*

Patients received apatinib at an initial dose of 500 mg once daily taken orally on an empty stomach in 28-day cycles and continued until disease progression, patient withdrawal, or unacceptable toxic effects. The protocol-defined dose modification criteria were as follows: when grade 3 hematological toxicity occurs in the patient, the drug should be suspended (for no longer than 2 weeks) and the original dose continued when the adverse reactions return to  $\leq$  grade 2; if  $\geq$  grade 3 adverse toxicity occurs again, the dose of apatinib should be reduced to 250 mg (if grade 4 hematological toxicity occurs, the dose of apatinib should be immediately reduced to 250 mg); when grade 3 non-hematological toxicity occurs in the patient, the original dose should be continued after the adverse reaction is restored to  $\leq$  grade 1; if  $\geq$  grade 3 adverse reactions occur again, the dose of apatinib should be reduced to 250 mg.

Clinical, laboratory assessments, and QOL were performed at baseline and at one-month interval. Patients were provided with a blood pressure (BP) monitoring device and instructed to measure their BP once daily. Tumor assessments were performed at baseline and every month using RECIST 1.1 criteria. Objective responses were confirmed at least 4 weeks after initial documentation. Adverse events (AEs) were graded by the Common Terminology Criteria for Adverse Events (CTCAE v5.0). QOL was assessed by the European Organization for

Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) and the head and neck 35 module (H&N35).

#### *Sample size estimation*

Simon's Minimax two-stage phase II design was used to calculate the sample size [13]. We considered the study drug to be inactive if CBR was  $\leq 15\%$ , and considered the study drug as active if CBR was  $\geq 35\%$ . Assuming the type I error of 0.05 and the type II error of 0.15, the sample size and stopping rule were as follows: accrue 16 patients in stage I; if 3 or fewer of the 16 patients were nonprogressors, we would stop the study and conclude the study drug as inactive, otherwise proceed to stage II and accrue an additional 30 patients. After stage I interim analysis, the study proceeded to stage II and recruited a total of 19 patients but stopped for poor accrual.

#### *Statistical analysis*

We analyzed efficacy and safety in the intention-to-treat population. CBR was calculated with the corresponding exact 95% two-sided confidence interval (95% CI) using standard methods based on the binomial distribution. Time-to-event data were summarized using the method of Kaplan–Meier. Paired Student's t-tests or Wilcoxon rank tests were used to compare QOL scores before and after treatment of apatinib. All statistical analyses were performed with SPSS18.0 (SPSS, Chicago, IL, USA). Results were considered statistically significant with a P-value  $< 0.05$ .

## **Results**

#### *Patients characteristics*

Between Aug 2017 and Apr 2019, 19 patients were enrolled in this study (Table 1). All patients were ECOG 0–2, with a median age of 48 years (range, 23–64 years). Four (21.1%) patients developed local-regional recurrent disease, 10 (52.6%) had only distant metastasis and 5 (26.3%) patients had both. The distant metastases were as follows: 5 (26.3%) liver metastasis, 7 (36.8%) lung metastasis, 6 (31.6%) bone metastasis, 3 (15.8%) distant lymph node metastasis, and 7 (36.8%) multi-organ metastases. Eleven patients (57.9%) patients had previously received one line of chemotherapy and seven (36.8%) patients received second-line of

**Table 1** Baseline patient characteristics (N=19)

Characteristic	Number of patients (%)
Age, years	48 [23–64]
Sex	
Female	4 (21.1)
Male	15 (78.9)
ECOG performance status	
0	11 (57.9)
1	7 (36.8)
2	1 (5.3)
Metastasis number	
0	4 (21.0)
1–2	12 (63.2)
3	3 (15.8)
Recurrent or metastasis sites	
Recurrent disease	4 (21.1)
Distant metastasis	10 (52.6)
Recurrent and distant metastasis	5 (26.3)
Liver	5 (26.3)
Lung	7 (36.8)
Bone	6 (31.6)
Distant lymph nodes	3 (15.8)
Multiple metastatic sites	7 (36.8)
Previous lines of therapy for recurrent/metastasis disease	
1	11 (57.9)
2	7 (36.8)
3 or more	1 (5.3)

ECOG: Eastern Cooperative Oncology Group.

chemotherapy for the treatment of recurrent/metastatic disease.

### Treatment responses

Tumor measurements were carried out monthly. There were no cases of complete response and two (10.5%) patients showed a partial response to treatment. Eight (42.1%) patients achieved stable disease, while six (31.6%) had progressive disease. Three patients could not be evaluated

for disease status because they had no post-baseline efficacy assessment. The CBR was 52.6% (95% CI: 29.8–76.2%) at 3 months.

Four (21.1%) patients received more than 6 months of treatment and the disease remained stable at 6 months. There was a reduction in tumor size in 42.1% of subjects at best response assessment (*Figure 1*). At the last follow-up visit, six (31.6%) patients had disease progression and 12 (63.2%) patients had died. The median PFS and OS were 3.7 (95% CI: 0.6–6.8) months and 12.9 (95% CI: 9.3–16.5) months, respectively (*Figure 2*). Subgroup analysis showed the AE of hand-foot syndrome was an independent prognostic factor for PFS [hazard ratio (HR) = 0.163, 95% CI: 0.028–0.934, P=0.042].

### Toxicities

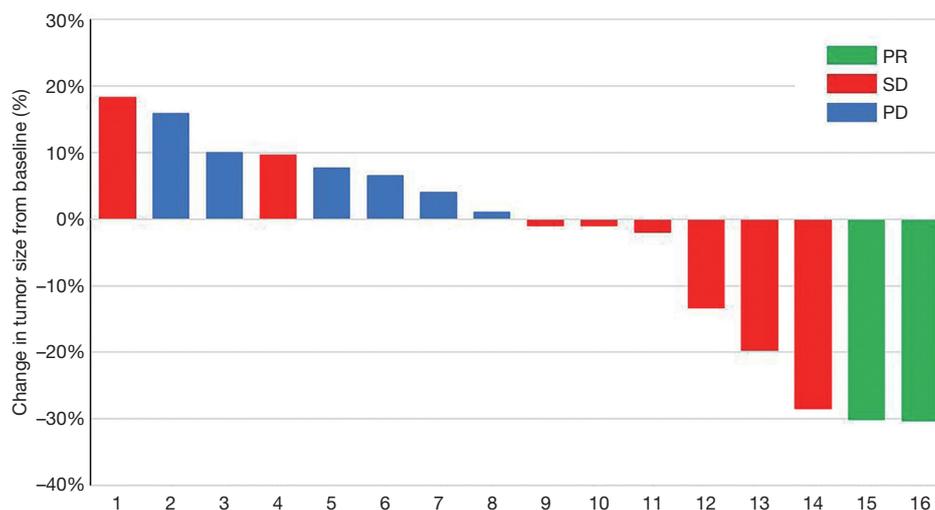
Treatment-related AEs are listed in *Table 2*. Most patients developed grade 1–2 acute toxicities. In the intention-to-treat population, grade 3–4 AEs included: hand-foot syndrome [3 (15.8%)], neutropenia [2 (10.5%)], proteinuria [2 (10.5%)], oral mucosal pain [2 (10.5%)], hypertension [1 (5.3%)], hyponatremia [1 (5.3%)], artery dissection [1 (5.3%)], and nasopharyngeal hemorrhage [1 (5.3%)]. A serious AE was reported in one patient who died of nasopharyngeal hemorrhage. Six (31.6%) patients required dose reductions from 500 mg to 250 mg, which were related to proteinuria (n=2), hand-foot syndrome (n=2), epistaxis (n=1), and anorexia (n=1). Termination of medication occurred in two patients due to nasopharyngeal hemorrhage and arterial dissection. The median dose of apatinib was 357.9 mg in this patient cohort.

### Quality of life

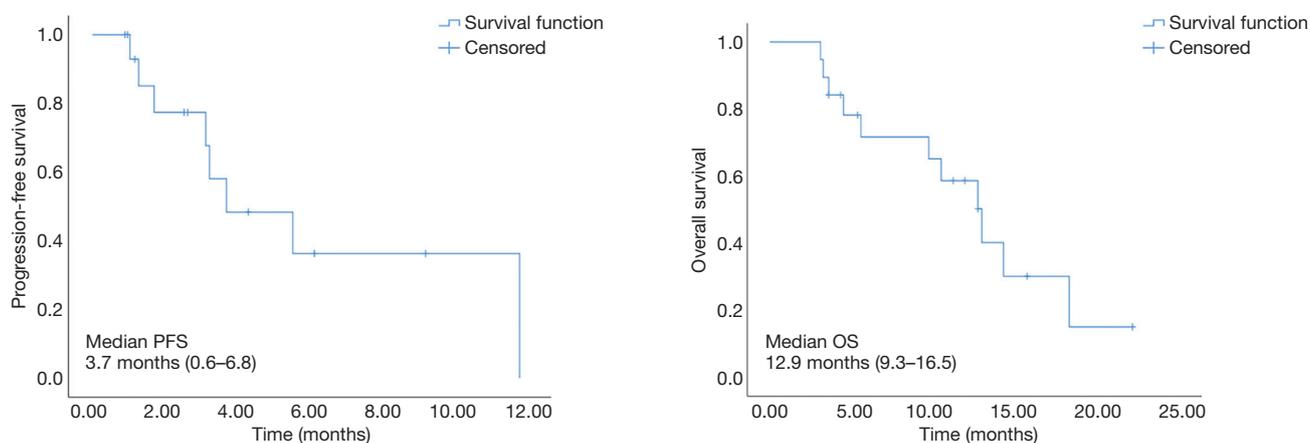
The changes in patient-reported QOL before and after treatment are shown in *Table 3*. There was no clinically meaningful deterioration in QOL following treatment with apatinib as measured by the EORTC QLQ-C30 except for nausea & vomiting (6.7 vs. 16.7, P=0.014; *Figure 3A,B*). Based on the EORTC QLQ-H&N35, clinically meaningful worsening was seen in the domains of pain after treatment (pain: 6.1 vs. 23.4, P=0.001; *Figure 3C*).

### Discussion

The prognosis of patients with recurrent or metastatic NPC remains poor, with a median PFS of 4–10 months (12), and



**Figure 1** Waterfall plot for the best percentage change in target lesion size is shown for 16 patients who had at least one post-baseline efficacy assessment. The color indicates type of response. PR, partial response; SD, stable disease; PD, progressive disease.



**Figure 2** Kaplan-Meier survival curves of progression-free survival (PFS) and overall survival (OS).

there is currently no standard, effective treatment strategy for those who experience treatment failure after first-line platinum-based chemotherapy. The use of molecular targeted agents may be a promising strategy for this patient cohort. To the best of our knowledge, this is the first clinical study to evaluate the efficacy and safety of apatinib in treating patients with recurrent or metastatic NPC who failed prior platinum-based chemotherapy.

Several multi-kinase inhibitors (including sorafenib, pazopanib, axitinib, and sunitinib) have been investigated in recurrent or metastatic NPC (6-9). For example, pazopanib (an inhibitor of VEGFR-1, -2, and -3, PDGF-a, PDGF-b, and c-kit tyrosine kinase) was shown to have encouraging

activity (CBR of 54.5% and median PFS of 4.4 months) in heavily pretreated patients with recurrent or metastatic NPC (9). In addition, dynamic-contrast enhanced computed tomography showed significant reductions in tumor blood flow with pazopanib treatment (7). Meanwhile, in another study, 13 patients with recurrent or metastatic NPC were treated with sunitinib monotherapy as a second-line chemotherapy, with modest results: the CBR was 28.6% and the median PFS was 3.5 months (9). Axitinib was also found to have modest disease control in NPC (6).

Apatinib is a highly-selective VEGFR-2 inhibitor, which has shown to be an effective treatment in advanced stomach cancer, colorectal cancer and non-small cell lung cancer

**Table 2** Treatment-related adverse events (according to CTCAE v5.0)

	Grade 1–2, n (%)	Grade 3, n (%)	Grade 4–5, n (%)	All grades, n (%)
<b>Non-hematological</b>				
Hypertension	8 (42.1)	1 (5.3)	0	9 (47.4)
Proteinuria	10 (52.6)	2 (10.5)	–	12 (63.2)
Hand-foot syndrome	7 (36.28)	3 (15.8)	–	10 (52.6)
Fatigue	18 (94.7)	0	–	18 (94.7)
Oral mucosal pain	4 (21.1)	2 (10.5)	0	6 (31.6)
Nausea/Vomiting	6 (31.6)	0	0	6 (31.6)
Anorexia	10 (52.6)	0	0	10 (52.6)
Diarrhea	6 (31.6)	0	0	6 (31.6)
QTc interval prolongation	2 (10.5)	0	0	2 (10.5)
Arterial dissection	0	1 (5.3)	0	1 (5.3)
Epistaxis	5 (26.3)	–	1 (5.3)	6 (31.6)
APTT prolongation	5 (26.3)	0	–	5 (26.3)
Weight loss	3 (15.8)	0	–	3 (15.8)
Hypoalbuminemia	5 (26.3)	0	0	5 (26.3)
Hyperbilirubinemia	6 (31.6)	0	0	6 (31.6)
Elevated creatinine	2 (10.5)	0	0	2 (10.5)
Elevated alanine aminotransferase	4 (21.1)	0	0	4 (21.1)
Elevated aspartate aminotransferase	8 (42.1)	0	0	8 (42.1)
Hyponatremia	3 (15.8)	1 (5.3)	0	4(21.1)
<b>Hematological</b>				
Leukopenia	2 (10.5)	0	0	2 (10.5)
Neutropenia	8 (42.1)	2 (10.5)	0	10 (52.6)
Anemia	10 (52.6)	0	0	10 (52.6)
Thrombocytopenia	6 (31.6)	0	0	6 (31.6)

APTT, activated partial thromboplastin time.

(13–15). In addition, apatinib was shown to inhibit tumor growth and have synergistic effects with chemotherapy in a nude mice model xenografted with CNE-2 NPC cells (10). In the present study, we observed apatinib had modest anti-cancer activity with a CBR of 52.6%, a median PFS of 3.7 months, and a median OS of 12.9 months. Four (21.1%) patients received more than 6 months of treatment and the disease remained stable at 6 months. Most patients had stable disease, which is consistent with its proposed antiangiogenesis mechanism of action. The efficiency of apatinib was comparable to other multi-kinase inhibitors

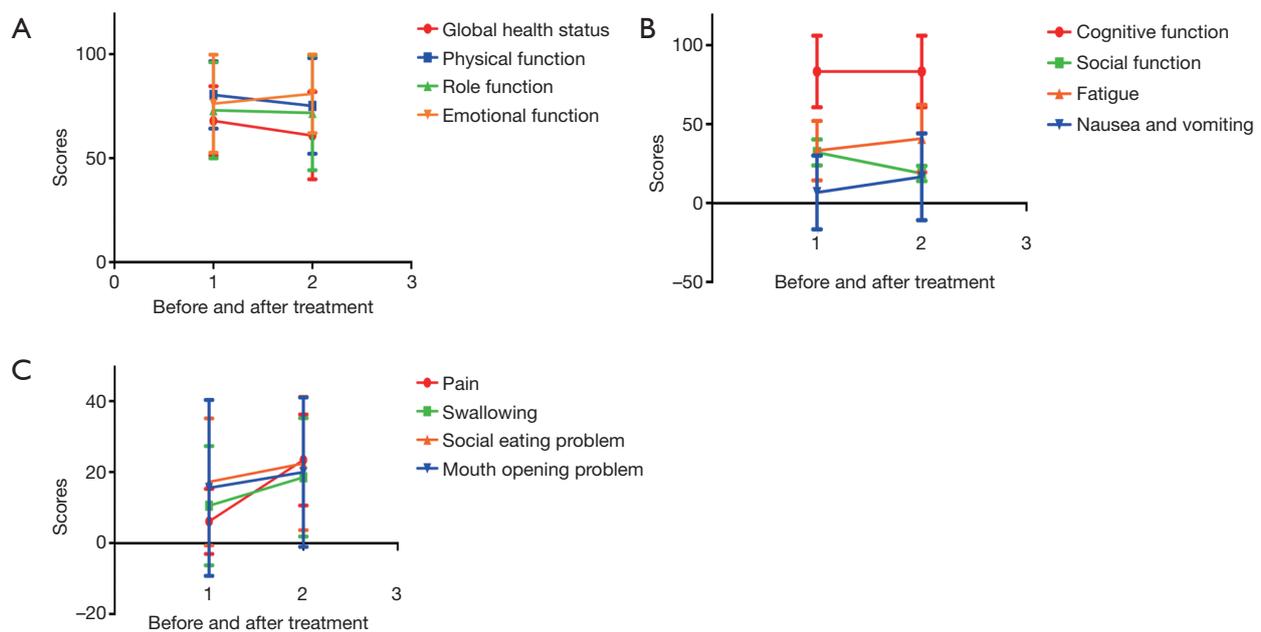
mentioned above (6–7,9).

Unfortunately, there was an unsatisfactory tolerance to apatinib, with 50% of patients requiring dose adjustment due to apatinib-related AEs. This resulted in a reduced dose of apatinib, which may have limited its overall efficacy. Indeed, our results suggest that apatinib at an initial dose of 500 mg once daily taken orally may not be optimal for recurrent or metastatic NPC who failed prior cisplatin-based chemotherapy. Therefore, the optimal dose of apatinib and combined treatment mode should be explored in future. Notwithstanding, apatinib showed a relatively satisfactory

**Table 3** EORTC QLQ-C30 and H&N35 scores comparison before and after treatment (mean  $\pm$  standard deviation)

	Scales	N	Before treatment	After treatment*	d	t value	P value	
EORTC QLQ-C30	Global health status	13	67.95 $\pm$ 16.61	60.90 $\pm$ 21.08	7.05	1.821	0.094	
	Physical functioning	15	80.44 $\pm$ 16.23	75.11 $\pm$ 23.02	-5.33	1.023	0.324	
	Role functioning	13	73.08 $\pm$ 23.11	71.80 $\pm$ 27.54	-1.28	0.322	0.753	
	Emotional functioning	14	76.19 $\pm$ 23.54	80.95 $\pm$ 18.90	4.76	-0.9	0.385	
	Cognitive functioning	15	83.33 $\pm$ 22.71	83.33 $\pm$ 22.71	0	0	1	
	Social functioning	15	32.04 $\pm$ 8.27	18.76 $\pm$ 4.84	-13.28	-0.661	0.519	
	Fatigue	12	33.22 $\pm$ 18.87	40.83 $\pm$ 21.41	7.61	-1.327	0.211	
	Nausea and vomiting	15	6.67 $\pm$ 23.40	16.67 $\pm$ 27.46	-10	-2.806	0.014	
	Dyspnea	15	6.67 $\pm$ 25.82	8.89 $\pm$ 19.79	2.22	-0.435	0.67	
	Insomnia	15	11.11 $\pm$ 27.22	15.56 $\pm$ 24.78	4.45	-0.619	0.546	
	Appetite loss	15	20.00 $\pm$ 32.85	28.89 $\pm$ 27.79	8.89	-1.293	0.217	
	Constipation	15	6.67 $\pm$ 22.54	15.55 $\pm$ 24.77	8.88	-1.169	0.262	
	Diarrhea	14	4.76 $\pm$ 12.10	11.90 $\pm$ 21.11	7.14	-1.147	0.272	
	Financial difficulties	15	62.22 $\pm$ 41.53	57.78 $\pm$ 34.43	-4.44	0.564	0.582	
	Pain	15	6.11 $\pm$ 9.16	23.44 $\pm$ 12.86	17.33	-3.953	0.001	
	Swallowing	15	10.55 $\pm$ 16.81	18.51 $\pm$ 16.71	7.96	-1.649	0.121	
	Sensory problems	15	14.45 $\pm$ 15.26	11.67 $\pm$ 14.70	-2.78	0.543	0.596	
	Speech problems	15	14.15 $\pm$ 17.11	18.51 $\pm$ 13.85	4.36	-1.333	0.204	
	EORTC H&N35	Social eating problems	15	17.22 $\pm$ 17.95	22.44 $\pm$ 18.76	5.22	-1.097	0.291
		Social contact problems	15	15.44 $\pm$ 17.14	18.22 $\pm$ 19.59	2.78	-0.755	0.463
Less sexuality		14	40.48 $\pm$ 33.15	45.24 $\pm$ 30.96	4.76	-1.295	0.218	
Teeth		15	22.22 $\pm$ 32.53	20 $\pm$ 21.08	-2.22	0.323	0.751	
Mouth opening problems		15	15.56 $\pm$ 24.78	20.00 $\pm$ 21.08	4.44	-0.564	0.582	
Dry mouth		15	42.22 $\pm$ 29.46	37.78 $\pm$ 27.79	-4.44	0.619	0.546	
Sticky saliva		15	33.33 $\pm$ 28.17	33.33 $\pm$ 25.20	0	0	1	
Coughing		15	15.55 $\pm$ 21.33	15.55 $\pm$ 21.33	0	0	1	
Feeling ill		15	37.78 $\pm$ 27.79	33.33 $\pm$ 28.17	-4.45	0.521	0.61	
Painkillers		15	8.89 $\pm$ 15.26	11.11 $\pm$ 16.26	2.22	-1	0.334	
Nutritional supplements		15	6.67 $\pm$ 13.80	8.89 $\pm$ 15.26	2.22	-0.435	0.67	
Feeding tube		15	0 $\pm$ 0	0 $\pm$ 0	0	NA	NA	
Weight loss	15	15.55 $\pm$ 17.21	13.33 $\pm$ 16.90	-2.22	0.435	0.67		
Weight gain	15	0 $\pm$ 0	0 $\pm$ 0	0	NA	NA		

EORTC QOL-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QOL-H&N35, The EOTRC Quality of Life Questionnaire-Head and Neck 35. NA, none. \*, The score in the functional area after treatment is the highest score after the treatment cycle, and the score in the symptom area is the lowest score after the treatment cycle.



**Figure 3** The QOL scores of patients before and after treatment of apatinib. (A) Adjusted mean change in global health status, physician function, role function and emotional function according to EORTC QLQ-C30. (B) Adjusted mean change in cognitive function, social function, fatigue and nausea & vomiting according to EORTC QLQ-C30. (C) Adjusted mean change in pain, swallowing, social eating problem and month opening problem according to EORTC H&N35. EORTC QOL-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QOL-H&N35, The EOTRC Quality of Life Questionnaire-Head and Neck 35; QOL, quality of life. \*,  $P < 0.05$ .

anti-tumor activity and could be used as a therapeutic recommendation for recurrent or metastatic NPC.

Bleeding is one of the most common adverse effects of antiangiogenic agents. In our study, six (31.6%) patients reported nasopharyngeal hemorrhage and one patient with recurrent NPC died. Admittedly, patients with recurrent NPC are prone to nasopharyngeal hemorrhage, potentially because these tumors are close to the internal carotid artery, and the ability to repair nasopharyngeal tissue after radiotherapy is poor. In our study, grade 3 to 4 hypertension, proteinuria and hand-foot syndrome occurred in 5.3%, 10.5% and 15.8% of patients, respectively. These toxicities of apatinib are similar to other multi-kinase inhibitors, including pazopanib and sunitinib (7,9). In addition, the presence of apatinib-associated hypertension, proteinuria and hand-foot syndrome in the first 4 weeks of treatment was shown to be associated with prolonged median OS (16). Similarly, in the present study, patients with hand-foot syndrome showed better PFS than those without (median PFS: 5.5 *vs.* 1.7 months;  $P = 0.042$ ). With regards to the patient-reported QOL outcomes, treatment

with apatinib did not significantly influence the functional and symptom domains, except for nausea & vomiting and pain (10 points or more deterioration,  $P < 0.05$ ). Therefore, the adverse effects of apatinib found in our study are considered moderate and acceptable when compared with historical reports of other antiangiogenic agents. Nonetheless, more attention should be paid to toxicity management when apatinib monotherapy or combined therapy is used in recurrent or metastatic NPC.

Whether combining antiangiogenic agents such as apatinib with other drugs improves their efficacy and reduces drug resistance is an area worth investigating. Preclinical studies have demonstrated that the use of antiangiogenic agents could convert the tumor microenvironment from an immunosuppressive one to one that is more immunosupportive (17). Indeed, combining low-dose apatinib treatment with anti-PD-L1 alleviated hypoxia, increased the infiltration of CD8<sup>+</sup> T cells and reduced recruitment of tumor-associated macrophages in a syngeneic lung cancer mouse model, resulting in significantly reduced tumor growth and prolonged survival (18).

Furthermore, in a phase I clinical study, SH1210 (an anti-PD-1 antibody) combined with apatinib showed encouraging efficacy in refractory hepatocellular cancer with an overall response rate of 50% (19). The anti-tumor activity of low-dose apatinib combined with anti-PD-1 in recurrent or metastatic NPC has also been observed in clinical practice. Therefore, the value of antiangiogenic-based combination therapy in NPC should be further investigated.

There are some limitations to our study. Due to the small sample size, these results should be interpreted with caution. In addition, due to the required dose reduction resulting from adverse effects, our study may not have revealed the maximal effect of this drug. Therefore, a larger clinical study is warranted to establish the optimal treatment mode of apatinib for recurrent or metastatic NPC.

## Conclusions

Apatinib achieved modest disease control with acceptable toxicity in recurrent/metastatic NPC patients pretreated with platinum-based chemotherapy. A prospective, clinical trial is warranted to confirm the efficacy of apatinib in a large group of NPC patients, with a better defined dose schedule or as a combination therapy.

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## Footnote

*Reporting Checklist:* The authors have completed the TREND reporting checklist. Available at <http://dx.doi.org/10.21037/tcr-20-1773>

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of Zhejiang Cancer Hospital (NO.: IRB-2017-126) and informed consent was taken from all the patients.

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