Original Article

The efficacy and safety of apatinib in patients with recurrent or metastatic nasopharyngeal carcinoma: a systematic review and meta-analysis

Huixiong Lin[1#], Xiangqian Weng[2#], Xiangji Wu[3], Lizhong Wu[3]

[1]Department of Internal Medicine-Oncology, Qionghai People's Hospital, Qionghai, China; [2]Department of Radiotherapy, The First Affiliated Hospital of Hainan Medical University, Haikou, China; [3]Department of Otolaryngology Head and Neck Surgery, Qionghai People's Hospital, Qionghai, China

Contributions: (I) Conception and design: H Lin, X Weng, L Wu; (II) Administrative support: X Wu; (III) Provision of study materials or patients: H Lin, X Weng, L Wu; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: H Lin, X Weng, L Wu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Lizhong Wu. Department of Otolaryngology Head and Neck Surgery, Qionghai People's Hospital, No. 33, Fuhai Road, Jiaji Town, Qionghai 571400, China. Email: wlz268@163.com.

Background: Apatinib is a small-molecule tyrosine kinase inhibitor targeting VEGFR-2, which was recently used in a phase II clinical trial for the treatment of recurrent or metastatic nasopharyngeal carcinoma (rmNPC). However, there is no consistent conclusion on its efficacy and safety on rmNPC. This study conducted a meta-analysis of clinical research on the efficacy and safety of apatinib in the treatment of rmNPC.

Methods: In April 2022, the PubMed, Web of Science, Scopus, Chinese National Knowledge Infrastructure (CNKI), CMB, and Wanfang databases were systematically searched, and relevant research literature were screened and analyzed. The clinical trial literatures using apatinib as the main single or combined treatment for rmNPC patients were selected and combined with objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and other efficacy and safety indicators.

Results: The meta-analysis included 12 studies, including 408 patients with rmNPC. The methodological index for nonrandomized studies scale was used to evaluate the bias of the included literatures and found that the bias was low. A total of 408 rmNPC patients were included in the included literature, with 11 studies being a phase II single-arm trial and one being a phase II non-randomized controlled trial. The ORR of patients with rmNPC treated with apatinib was 41.5% (95% CI: 34.8%, 48.2%), and the DCR was 80.2% (95% CI: 70.9%, 89.6%). The median PFS was 6.4 months (95% CI: 5.3, 7.4), and the median OS was 14.8 months (95% CI: 10.7, 18.9). The incidence of hypertension, hand-foot skin reaction, and proteinuria was 31% (95% CI: 19–43%), 29% (95% CI: 20–39%), and 13% (95% CI: 6–20%), respectively.

Discussion: The efficacy of apatinib in the treatment of rmNPC patients is similar to that of the previous second-line chemotherapy drugs, but since most studies are phase II single-arm studies, the advantages and disadvantages of the existing second-line chemotherapy regimens cannot be determined.

Keywords: Apatinib; recurrent nasopharyngeal carcinoma; metastatic nasopharyngeal carcinoma; meta-analysis

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Introduction

Nasopharyngeal carcinoma (NPC) is a common head and neck malignancy in southern China and Southeast Asia with prominent regional and ethnic epidemiological characteristics (1). NPC is very sensitive to platinum-based chemotherapy and radiotherapy; however, 15–30% of patients still have distant metastasis after radical treatment, and this is known as recurrent or metastatic NPC (rmNPC) (2). The treatment of rmNPC includes chemotherapy, radiotherapy, radioactive particle therapy, radiofrequency ablation, targeted drug delivery, and immunotherapy (3,4). Once rmNPC has occurred, the sensitivity and therapeutic effect of radiotherapy and chemotherapy drugs (such as gemcitabine cisplatin) are reduced (5). Although platinum-based combination chemotherapy is the recognized first-line treatment for rmNPC, there is no standard clinical treatment for patients who experience platinum-based treatment failure (6). Apatinib is a novel tyrosine kinase inhibitor of blood vascular endothelial growth factor receptor 2 (VEGFR-2) that selectively targets intracellular adenosine triphosphate (ATP) binding sites and has shown efficacy in a variety of solid tumors (7-9). In recent years, some clinical trials have explored the efficacy and safety of apatinib in the treatment of rmNPC. A phase II clinical single-arm study conducted by Kong *et al.* (10) showed that apatinib monotherapy has a certain curative effect on rmNPC. However, the objective response rate and disease control rate were low, and there was no significant improvement compared with the existing second-line therapy. In a clinical controlled trial conducted by Pan *et al.* (11), the efficacy of apatinib combined with gemcitabine-cisplatin regimen was significantly higher than that of the control group. However, the incidence of hypertension in the treatment group was 63.6%, and the incidence of hand-foot syndrome was 22.3%, which were higher than those in the control group. Due to the small sample size and limited scope of a single study, there has not been a unified conclusion on its efficacy and safety, and no studies have organized and reviewed relevant clinical trials. In the absence of large-scale clinical trials of apatinib efficacy and safety, meta-analysis is an alternative approach to obtain relatively accurate assessments of apatinib efficacy and safety. Therefore, this study aimed to conduct a meta-analysis of clinical research on the efficacy and safety of apatinib in the treatment of rmNPC. We present the following article in accordance with the PRISMA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1467/rc).

Methods

Literature retrieval

We searched the PubMed, Web of Science, Scopus, Chinese National Knowledge Infrastructure (CNKI), CMB, and Wanfang databases in April 2022. The search language was limited to Chinese and English. The search terms were as follows: "apatinib"[Supplementary Concept] AND ("nasopharyngeal carcinoma"[MeSH Terms] OR ("nasopharyngeal"[Title/Abstract] AND "carcinoma"[Title/Abstract]) OR "nasopharyngeal carcinoma"[Title/Abstract] OR ("carcinoma"[Title/Abstract] AND "nasopharyngeal"[Title/Abstract]) OR "carcinoma nasopharyngeal"[Title/Abstract]).

Inclusion and exclusion criteria

The inclusion criteria were as follows: (I) participants: rmNPC patients; (II) interventions: use of apatinib as the primary single or combination therapy; (III) comparisons: without apatinib as a control for the primary single or combination therapy, no control for single-arm studies; (IV) outcomes: the study included 1 or more main observation indicators, such as objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), clinical benefit rate (CBR), and 1-year survival rate; 1 or more efficacy indicators, such as 2-year survival rate; and 1 or more safety indicators, such as adverse reactions and toxicity; and (V) study design: Types of clinical trials such as randomized controlled trials and single-arm trials with more than 10 patients treated, rather than case report studies.

The exclusion criteria were as follows: (I) the content of the study deviated from the aims of this paper; (II) duplicated data or literature; (III) literature that did not contain data; and (IV) literature that did not have original text.

Data sorting

One researcher independently extracted the contents of the included literature, and 2 researchers independently checked the extracted content. The extracted contents included study author, year of development, year of publication, type of study, patient inclusion criteria, number of patients, main observation indicators, and other information.

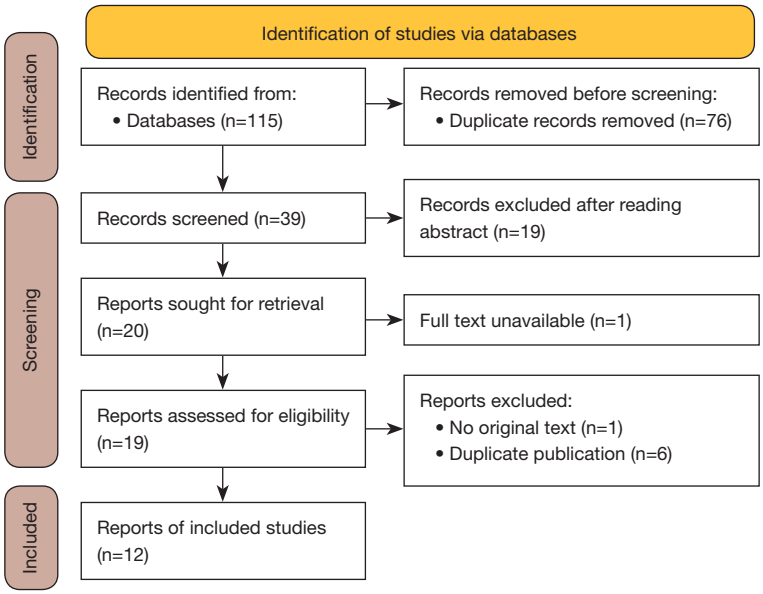

Figure 1 Document screening flow chart.

Risk of bias assessment

Since this study was a single-arm, nonrandomized clinical trial, the methodological index for nonrandomized studies (MINORS) scale was used for evaluation. The ideal score is 16 for single-arm studies and 24 for nonrandomized controlled trials. When a single-arm study scored less than 12 and a non-randomized controlled study with a score of less than 20, the risk was considered high.

Statistical analysis

All data in this study were analyzed using Stata version 16.0 (StataCorp LLC, College Station, TX, USA). $P<0.05$ was considered statistically significant, and all tests were two-sided. The stata command metaprop was used to estimate the standard error of a single rate by the scoring method, and to combine the single-group design rates (or proportions) such as ORR and DCR. Then use the metan command to merge single-group design measurement data (usually median and 95% CI) such as PFS and OS. For the safety evaluation, the more comprehensive indicators reported in adverse reactions (hypertension, hand-foot skin reaction, and the incidence of proteinuria) were used as the effect size for statistical analysis. The heterogeneity test between different studies was quantified using statistic I^2, $I^2=100\% \times (Q - df)/Q$. When I^2 was ≥50%, it was determined that there was heterogeneity between the different studies. When I^2 (corrected for degrees of freedom) was less than 50%, it was judged that there was no heterogeneity between the different studies. All results were meta scored by the random-effects model. Funnel plots and Egger's test were used to test for publication bias.

Results

Literature search

The document screening process of this study is shown in *Figure 1*. A total of 115 relevant Chinese and English documents were retrieved from 6 databases. After removing 76 duplicate papers, 19 papers with weak correlation were screened out by reading the title and abstract, and the remaining 20 papers were read. Among these papers, 1 had no full text available, 1 had no original text, and 6 were duplicate publications. Therefore, 12 studies were finally included.

Basic information included in the study

Table 1 shows the basic information of the 12 included studies. Among them, 11 studies were phase II single-arm trials, and 1 study was a phase II nonrandomized controlled trial. Therefore, our study focused on analyzing patient data on the efficacy and safety of apatinib in the treatment rmNPC. A total of 408 patients with rmNPC aged 21 to

Table 1 Basic information of the patients included in the study

Author, year	Research type	Inclusion criteria	Main observation indexes	Year	Number of patients treated (control)	Age [median (range) or mean ± SD], years
Cai *et al.*, 2020 (12)	Phase II single arm	Patients in the Department of Oncology of Zhongshan University aged 18–70 with at least 1 failed chemotherapy regimen, an ECOG score of 0–2, and life expectancy ≥3 months	ORR, DCR, PFS, OS	2018–2020	54	46 (22–68)
Huang *et al.*, 2021 (13)	Phase II single arm	Patients in Chongqing University Cancer Hospital with metastasis after radiotherapy/chemotherapy	ORR, PFS, OS	2016–2019	35	52 (21–71)
Liya *et al.*, 2020 (14)	Phase II single arm	Patients with lung and/or liver metastasis of NPC who failed first-line and follow-up treatment in Hainan General Hospital. Age ≥18 years old, clear pathological diagnosis, Karnofsky physical fitness score ≥80, no nasopharyngeal recurrence, life expectancy ≥3 months, previously received paclitaxel or gemcitabine combined with platinum-based therapy	ORR, PFS, OS	2015–2017	41	48 (23–67)
Ruan *et al.*, 2021 (15)	Phase II single arm	Patients with rmNPC in the Affiliated Hospital of Guilin Medical University, Wuzhou Red Cross Hospital, and Guilin Nanxishan Hospital who had previously received at least 1 chemotherapy regimen	ORR, PFS, OS	2017–2018	33	48(23–70)
Tao *et al.*, 2020 (16)	Phase II single arm	Patients with rmNPC in Zhejiang cancer hospital who were confirmed by tissue or cytology and failed previous platinum-based chemotherapy	CBR, PFS, OS	2017–2019	19	48 (23–64)
Chen *et al.*, 2019 (6)	Phase II single arm	Patients with rmNPC in the First Affiliated Hospital of Nanchang University	ORR, DCR, PFS	2016–2017	16	53 (31–65)
Feng *et al.*, 2019 (17)	Phase II single arm	Patients with rmNPC in Xiping People's Hospital	ORR, DCR, PFS, OS	2016–2017	16	34–70
Kong *et al.*, 2019 (10)	Phase II single arm	Patients in the First Affiliated Hospital of Zhengzhou University who failed standard second-line treatment and were pathologically confirmed as NPC with measurable lesions	ORR, DCR, PFS, OS	2016–2019	66	30–77
Li *et al.*, 2020 (18)	Phase II single arm	Patients with rmNPC in Sichuan Cancer Hospital and the Affiliated Hospital of North Sichuan Medical College	PFS, OS	2017–2020	21	47 (29–69)
Pan *et al.*, 2020 (11)	Phase II non-randomized control	Patients with rmNPC in the First Affiliated Hospital of Zhengzhou University	ORR, DCR, PFS	2017–2018	22 (16)	t: 31–63; c: 32–68
Zhao *et al.*, 2021 (19)	Phase II single arm	Patients with metastatic NPC after chemotherapy and/or radiotherapy in Lichuan People's Hospital with an ECOG score of 0–2	ORR, DCR	2020	80	37–76, 55.28±2.41
Zuo, 2020 (20)	Phase II single arm	Patients with metastatic NPC in Xiangxi People's Hospital who had used platinum-based systemic chemotherapy at least once	ORR, DCR, PFS, OS	2017–2019	18	49.6±8.0

SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS; overall survival; CBR, clinical benefit rate; NPC, nasopharyngeal carcinoma; rmNPC, recurrent or metastatic NPC.

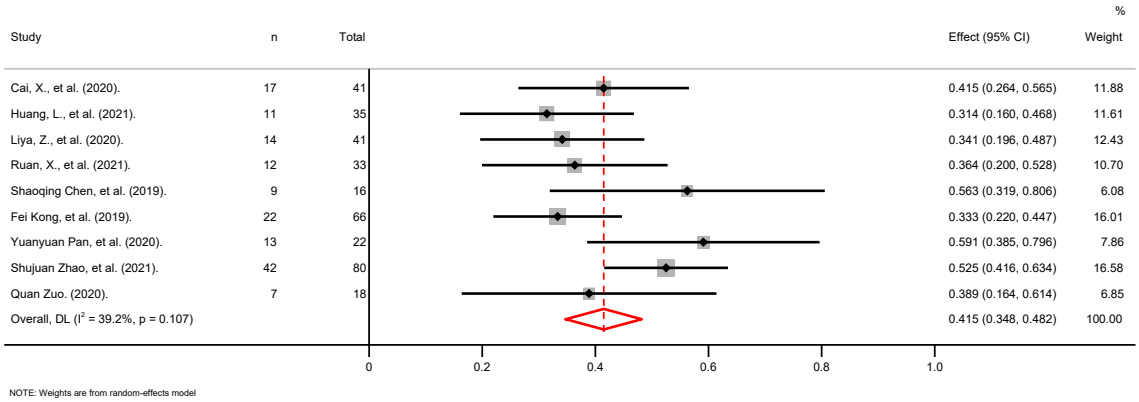

Figure 2 Forest plot of the combined ORR of patients with rmNPC treated with apatinib. ORR, objective response rate; rmNPC, recurrent or metastatic nasopharyngeal carcinoma.

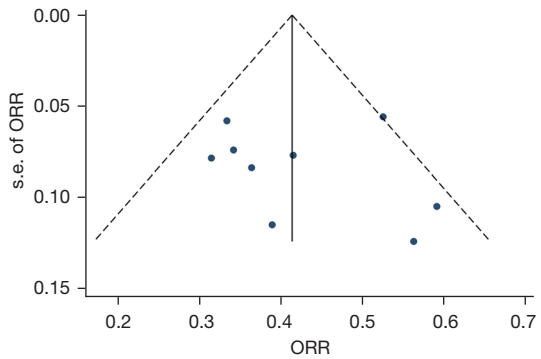

Figure 3 ORR funnel plot of patients with rmNPC treated with apatinib. ORR, objective response rate; rmNPC, recurrent or metastatic nasopharyngeal carcinoma.

77 were included in this meta-analysis. All the studies were conducted in China after 2015, and the included population was Chinese.

After the evaluation, 11 single-arm studies were included. Among these, 1 study scored 12 points, 8 studies scored 14 points, and 2 studies scored 16 points. One nonrandomized controlled trial was included, with a score of 22 points. Points were deducted mainly due to the prospective study size and a loss of follow-up rate of more than 5%.

Efficacy of apatinib treatment

ORR of patients with rmNPC treated with apatinib

ORR was reported in 9 of the included studies. We conducted a meta-analysis using a random-effects model, and the results showed that the total effect size of the 9 studies was 0.415 (95% CI: 0.348, 0.482). That is, the ORR of the apatinib treatment group was 41.5% (95% CI: 34.8%, 48.2%). There was little heterogeneity between the studies (I^2=39.2%, P=0.107; *Figure 2*). The points in the funnel chart were distributed on both sides within the CI in an inverted funnel shape, suggesting no obvious publication bias (*Figure 3*). Egger's test P=0.643.

DCR of patients with rmNPC treated with apatinib

DCR was reported in 9 of the included studies. We conducted a meta-analysis using a random-effects model, and the results showed that the total effect size of the 9 studies was 0.802 (95% CI: 0.709, 0.896). That is, the DCR of the apatinib treatment group was 80.2% (95% CI: 70.9%, 89.6%). There was significant heterogeneity between the studies (I^2=83.3%, P<0.001; *Figure 4*). The points in the funnel chart were scattered and Egger's test P=0.069 (*Figure 5*).

PFS in patients with rmNPC treated with apatinib

PFS was reported in 11 of the included studies. We conducted a meta-analysis using a random-effects model, and the results showed that the total effect size of the 11 studies was 6.4 (95% CI: 5.3, 7.4). That is, the median PFS in the apatinib treatment group was 6.4 months (95% CI: 5.3, 7.4). The heterogeneity between the studies was very large (I^2=98.6%, P<0.001). Egger's test P=0.033.

OS of patients with rmNPC treated with apatinib

OS was reported in 11 of the included studies. We conducted a meta-analysis using a random-effects model,

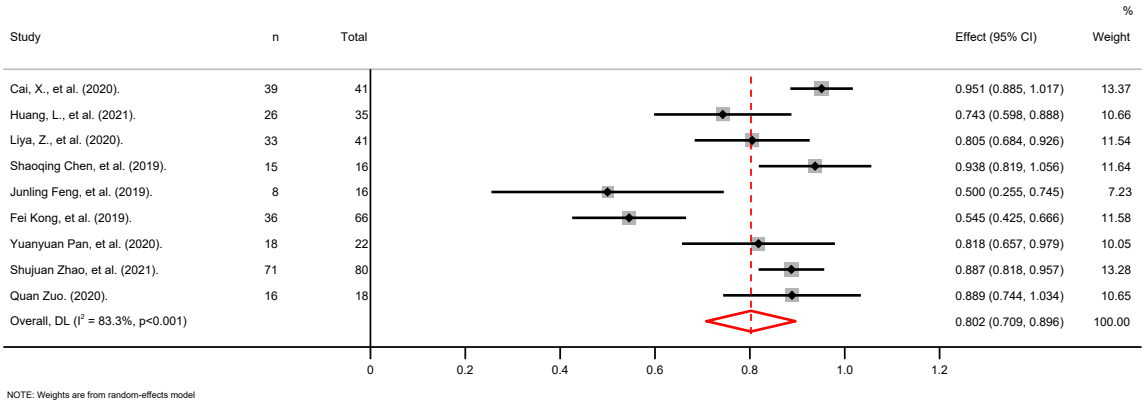

Figure 4 DCR forest plot of patients with rmNPC treated with apatinib. DCR, disease control rate; rmNPC, recurrent or metastatic nasopharyngeal carcinoma.

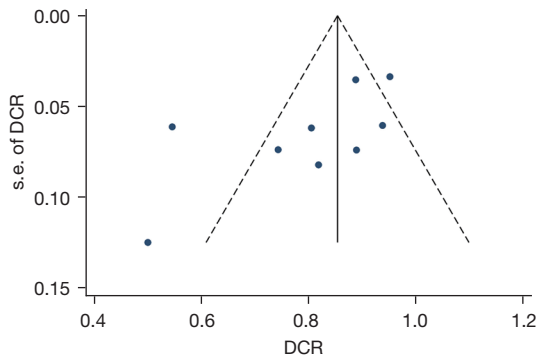

Figure 5 DCR funnel plot of patients with rmNPC treated with apatinib. DCR, disease control rate; rmNPC, recurrent or metastatic nasopharyngeal carcinoma.

and the results showed that the total effect size of the 11 studies was 14.8 (95% CI: 10.7, 18.9). That is, the median OS of the apatinib treatment group was 14.8 months (95% CI: 10.7, 18.9). The heterogeneity between the studies was very large (I^2=99.8%, P<0.001). Egger's test P=0.587.

Other indicators of patients with rmNPC treated with apatinib

In addition to the above indicators, CBR was reported in a study of 19 patients with rmNPC conducted by Tao *et al.* (52.6%) (16); 1-year survival rate was reported in a study of 21 patients with rmNPC conducted by Li *et al.* (53.2%) (18) and in a study of 33 patients with rmNPC conducted by Ruan *et al.* (81.8%) (15); and 2-year survival rate was reported in a study of 41 patients with rmNPC by Liya *et al.* (41.5%) (14) and in a study of 33 patients with rmNPC by Ruan *et al.* (21.2%) (15).

Safety of apatinib in the treatment of rmNPC

Adverse reactions after apatinib treatment were reported in all 12 included studies. The specific conditions of the adverse reactions in each study are shown in *Table 2*. Hypertension was the most frequently reported adverse reaction (12 studies), while hand-foot skin reaction and proteinuria were reported in 11 and 10 studies, respectively. In addition, dyslipidemia was reported in 2 studies (12,13), and cerebral infarction was reported in 1 study (13).

We conducted a meta-analysis of the 12 studies that reported the incidence of hypertension after apatinib treatment. One study with an incidence of 100% was excluded, and a random-effects model was selected due to significant heterogeneity between the studies (I^2=89.9%, P<0.001). The summarized incidence of hypertension in the remaining 11 studies was 31% (95% CI: 19–43%; *Figure 6*). Egger's test P=0.004.

We conducted a meta-analysis of the 11 studies that reported hand-foot skin reactions after apatinib treatment. One study with a 100% incidence was excluded, and a random-effects model was selected due to significant heterogeneity between the studies (I^2=77.7%, P<0.001). The summarized incidence of hand-foot skin reactions in the remaining 10 studies was 29% (95% CI: 20–39%; *Figure 7*). Egger's test P=0.463.

We conducted a meta-analysis of the 10 studies that reported the occurrence of proteinuria after apatinib treatment. One study with an incidence of 100% was excluded, and a random-effects model was selected due to

Table 2 Adverse reactions to apatinib in patients with rmNPC

Author, year	Total number	Anorexia, n [%]	Gastrointestinal reaction, n [%]	Hypertension, n [%]	Myelosuppression, n [%]	Fatigue, n [%]	Hand-foot skin reaction, n [%]	Oral pain/ mucositis, n [%]	Sore throat/ hoarseness, n [%]	Hemoptysis/ nosebleed, n [%]	Proteinuria, n [%]
Cai *et al.*, 2020 (12)	41	–	–	4 [10]	–	3 [7]	–	5 [12]	7 [17]	2 [5]	–
Huang *et al.*, 2021 (13)	35	7 [20]	2 [6]	11 [31]	18 [51]	11 [31]	9 [26]	6 [17]	–	6 [17]	9 [26]
Liya *et al.*, 2020 (14)	41	16 [39]	–	13 [32]	10 [24]	9 [22]	7 [17]	5 [12]	1 [2]	–	2 [5]
Ruan *et al.*, 2021 (15)	33	3 [9]	2 [6]	15 [45]	–	4 [12]	23 [70]	13 [39]	–	4 [12]	6 [18]
Tao *et al.*, 2020 (16)	19	–	–	1 [5]	2 [11]	–	3 [16]	2 [11]	–	1 [5]	2 [11]
Chen *et al.*, 2019 (6)	16	16 [100]	16 [100]	16 [100]	16 [100]	16 [100]	16 [100]	–	–	–	16 [100]
Feng *et al.*, 2019 (17)	16	–	–	5 [31]	–	–	4 [25]	–	–	–	1 [6]
Kong *et al.*, 2019 (10)	66	7 [11]	6 [9]	30 [45]	19 [29]	13 [20]	25 [38]	–	7 [11]	–	27 [41]
Li *et al.*, 2020 (18)	21	–	2 [10]	2 [10]	1 [5]	8 [38]	5 [24]	3 [14]	5 [24]	3 [14]	2 [10]
Pan *et al.*, 2020 (11)	22	–	6 [27]	14 [64]	13 [59]	–	5 [23]	–	–	–	1 [5]
Zhao *et al.*, 2021 (19)	80	–	7 [9]	8 [10]	–	–	16 [20]	–	–	8 [10]	4 [5]
Zuo, 2020 (20)	18	18 [100]	5 [28]	4 [22]	13 [72]	10 [56]	3 [17]	7 [39]	15 [83]	4 [22]	2 [11]

Gastrointestinal reactions included nausea, vomiting, diarrhea, and constipation. Myelosuppression included leukocytes, neutrophils, platelets, and hemoglobin reduction, and so on. When multiple similar indicators appear in a study, take the largest number (for example, the number of leukopenia and neutropenia in one article at the same time, take the one with the largest number for reporting). rmNPC, recurrent or metastatic nasopharyngeal carcinoma.

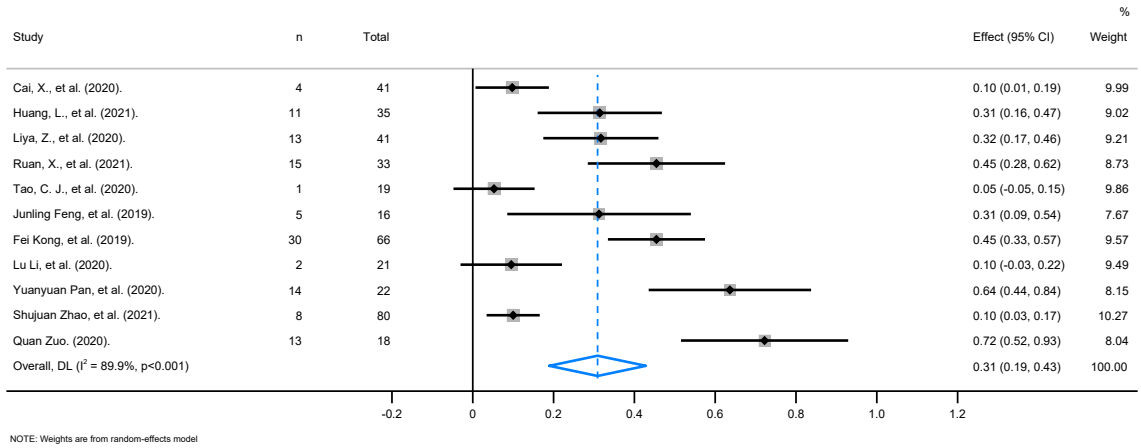

Figure 6 Incidence of hypertension in patients with rmNPC treated with apatinib. rmNPC, recurrent or metastatic nasopharyngeal carcinoma.

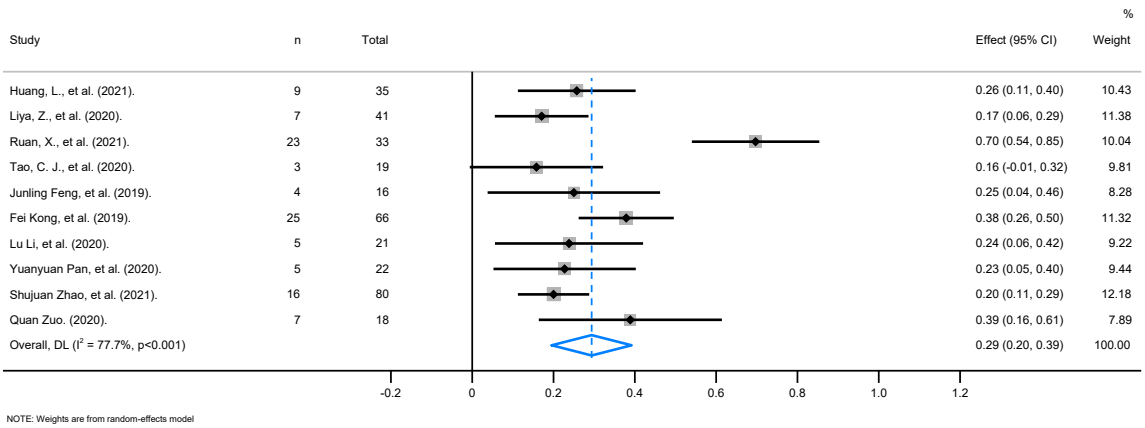

Figure 7 Incidence of hand-foot skin reactions in patients with rmNPC treated with apatinib. rmNPC, recurrent or metastatic nasopharyngeal carcinoma.

significant heterogeneity between the studies (I^2=80.1%, P<0.001). The summarized incidence in the remaining 9 studies was 13% (95% CI: 6–20%; *Figure 8*). Egger's test P=0.083.

Discussion

According to the International Agency for Research on Cancer (IARC), there were 129,079 new NPC cases in 2018, and NPC has a very specific geographic distribution, with more than 70% of new cases reported in East and Southeast Asia (21). In recent years, as a result of improvements in radiotherapy technology, the 5-year survival rate of patients with NPC has exceeded 80%, and the local and regional control rate has exceeded 90% (22,23). Distant metastasis is the most common cause of treatment failure in NPC, with lung and liver metastasis accounting for more than 70% of NPC deaths (22). Therefore, there is an urgent need to improve the efficacy of rmNPC treatment and reduce adverse reactions caused by treatment. Apatinib is a newly developed oral small molecule tyrosine kinase inhibitor targeting VEGFR-2. After VEGF binds to its receptor, it blocks downstream signal transmission and inhibits tumor angiogenesis, thereby inhibiting tumor growth (24). This study systematically reviewed the efficacy and safety of apatinib as a clinical chemotherapeutic drug for rmNPC to

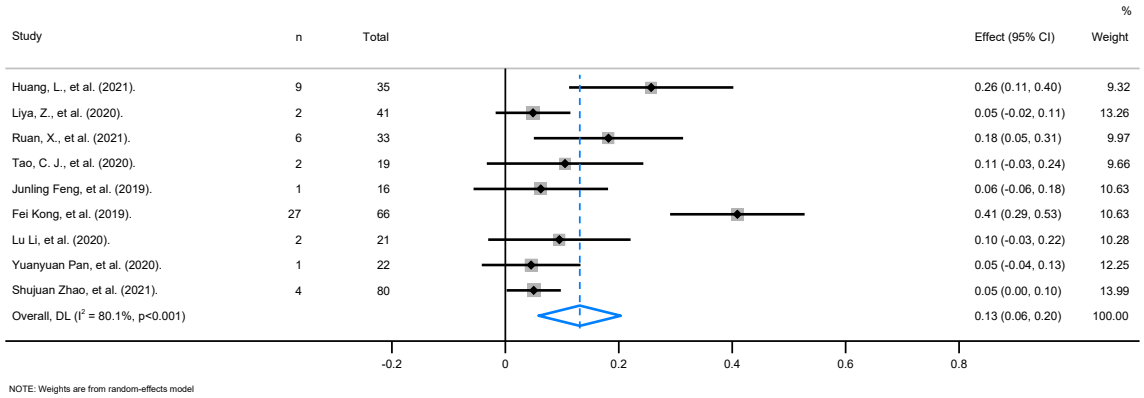

Figure 8 Incidence of proteinuria in patients with rmNPC treated with apatinib. rmNPC, recurrent or metastatic nasopharyngeal carcinoma.

provide evidence-based recommendations for the treatment of rmNPC.

Our meta-analysis included 12 studies and 408 patients with rmNPC. All the studies had a Chinese population and good internal consistency. As randomized controlled trials on apatinib treatment in rmNPC are still in progress, this meta-analysis included 1 phase II nonrandomized controlled trial and 11 single-arm studies. Therefore, we adopted a meta-analysis method suitable for single-arm studies and combined the rate and measurement data in a single study for analysis.

The results showed that the ORR and DCR of patients with rmNPC treated with apatinib were 41.5% (95% CI: 34.8–48.2%) and 80.2% (95% CI: 70.9–89.6%), respectively. The median PFS was 6.4 months (95% CI: 5.3–7.4), and the median OS was 14.8 months (95% CI: 10.7–18.9). The 2-year survival rate was only 15.0–34.4%, and the median OS was only 9.0–15.6 months. In previous studies of second-line treatment regimes in rmNPC, gemcitabine monotherapy had an ORR of 43.8%, a DCR of 71.9%, and a median OS of 16 months (25); capecitabine monotherapy had an ORR of 37% and a median OS of 14 months (26); gemcitabine combined with ifosfamide had an ORR of 37%, a median PFS of 6.7 months, and a median OS of 17.4 months (27); and gemcitabine combined with S-1 had an ORR of 37.7%, a median PFS of 5.2 months, and a median OS of 14.1 months (28). To sum up, the ORR and median PFS of commonly used second-line treatment regimes in rmNPC are about 40% and 5 months, respectively. Our results showed that apatinib had the same curative effect as previous second-line chemotherapy drugs. However, since most studies are phase II single-arm studies, it is not yet possible to determine the advantages and disadvantages of existing second-line chemotherapy regimes in rmNPC.

Clinically, the common adverse reactions of apatinib are myelosuppression toxicity, such as leucopenia, neutrophil, and thrombocytopenia, and nonhematological toxicity, such as fatigue, hypertension, hand-foot skin reaction, proteinuria, and oral ulcer. In our study, the most frequently reported adverse reactions were hypertension, hand-foot skin reaction, and proteinuria, with incidences of 31% (95% CI: 19–43%), 29% (95% CI: 20–39%), and 13% (95% CI: 6–20%), respectively.

This paper had the following limitations. First, most of the articles included in our meta-analysis were phase II single-arm trials that lacked control data, so it was not possible to make direct comparison between groups, and the level of evidence was relatively low. Second, there were some differences in each study's follow-up time, inclusion criteria, and treatment regime. Part of the study provided the efficacy and safety of apatinib in combination therapy for rmNPC. Therefore, there was a certain bias. Some effect measures showed publication bias, and thus more large sample studies are needed to verify the conclusions. Despite the above limitations, this meta-analysis of 12 clinical studies is the first to evaluate the efficacy and safety of apatinib in rmNPC. The results are relatively stable and representative of the population. More randomized controlled trials are needed to confirm the results of this paper.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1467/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1467/coif). The authors have no conflicts of interest to declare.

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.

References

1. Wong KCW, Hui EP, Lo KW, et al. Nasopharyngeal carcinoma: an evolving paradigm. Nat Rev Clin Oncol 2021;18:679-95.
2. Lee AW, Ma BB, Ng WT, et al. Management of Nasopharyngeal Carcinoma: Current Practice and Future Perspective. J Clin Oncol 2015;33:3356-64.
3. Masterson L, Howard J, Gonzalez-Cruz J, et al. Immune checkpoint inhibitors in advanced nasopharyngeal carcinoma: Beyond an era of chemoradiation? Int J Cancer 2020;146:2305-14.
4. Ng WT, Soong YL, Ahn YC, et al. International Recommendations on Reirradiation by Intensity Modulated Radiation Therapy for Locally Recurrent Nasopharyngeal Carcinoma. Int J Radiat Oncol Biol Phys 2021;110:682-95.
5. Zhang L, Huang Y, Hong S, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. Lancet 2016;388:1883-92.
6. Chen Shaoqing, Li Junhe, Yu Yongchun, et al. Efficacy and safety of gemcitabine combined with apatinib in second-line treatment of recurrent and metastatic nasopharyngeal carcinoma. Chinese Journal of Cancer Prevention and Treatment 2019;26:1547-50.
7. Jiang Q, Zhang NL, Ma DY, et al. Efficacy and safety of apatinib plus docetaxel as the second or above line treatment in advanced nonsquamous NSCLC: A multi center prospective study. Medicine (Baltimore) 2019;98:e16065.
8. Liao X, Li H, Liu Z, et al. Clinical efficacy and safety of apatinib in patients with advanced colorectal cancer as the late-line treatment. Medicine (Baltimore) 2018;97:e13635.
9. Li J, Qin S, Xu J, et al. Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Apatinib in Patients With Chemotherapy-Refractory Advanced or Metastatic Adenocarcinoma of the Stomach or Gastroesophageal Junction. J Clin Oncol 2016;34:1448-54.
10. Kong F, Ren L, Zhang F, et al. Efficacy and survival analysis of apatinib in the treatment of refractory nasopharyngeal carcinoma. China Oncology Clin 2019;46:1056-60.
11. Pan Y, Zhou P, Zhang X, et al. Clinical observation of apatinib combined with GP regimen in the treatment of recurrent advanced nasopharyngeal carcinoma. Journal of Medical Forum 2020;41:46-9.
12. Cai X, Li Z, Mai H, et al. Efficacy and safety of apatinib combined with capecitabine in patients with advanced nasopharyngeal carcinoma. Ann Oncol 2020;31:S672.
13. Huang L, Zhang X, Bai Y, et al. Efficacy and safety of apatinib in recurrent/metastatic nasopharyngeal carcinoma: A pilot study. Oral Oncol 2021;115:105222.
14. Zhou L, Lin J, Wu G. Safety and Feasibility of Low-Dose Apatinib Combined with S-1 as the Second-Line Therapy or Beyond in Chinese Patients with Pulmonary and Hepatic Metastasis of Nasopharyngeal Carcinoma. Drug Des Devel Ther 2020;14:1257-62.
15. Ruan X, Liang JH, Pan Y, et al. Apatinib for the treatment of metastatic or locoregionally recurrent nasopharyngeal carcinoma after failure of chemotherapy: A multicenter, single-arm, prospective phase 2 study. Cancer 2021;127:3163-71.
16. Tao CJ, Zhang P, Zhou L, et al. Apatinib in treating patients with recurrent or metastatic nasopharyngeal carcinoma who had failed prior platinum-based chemotherapy. Transl Cancer Res 2020;9:6392-401.
17. Feng J, Kong F, Zhang M. Effect of apatinib in the treatment of recurrent/metastatic nasopharyngeal

carcinoma. Henan Medical Research 2019;28:2586-8.
18. Li L, Xu P, Lai X, et al. A prospective, single-arm, multicenter phase II clinical study of apatinib maintenance therapy after chemoradiotherapy for metastatic nasopharyngeal carcinoma. China Cancer Prevention and Treatment 2020;12:397-402.
19. Zhao S, Luo L. Efficacy and safety of apatinib as maintenance monotherapy for metastatic nasopharyngeal carcinoma after chemotherapy. China Medical Abstracts (Otolaryngology) 2021;36:8-9.
20. Zuo Q. Clinical observation of apatinib combined with siggio in the treatment of metastatic nasopharyngeal carcinoma. Jishou: Jishou University, 2020.
21. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
22. Lee AW, Ng WT, Chan LL, et al. Evolution of treatment for nasopharyngeal cancer--success and setback in the intensity-modulated radiotherapy era. Radiother Oncol 2014;110:377-84.
23. Wang W, Feng M, Fan Z, et al. Clinical outcomes and prognostic factors of 695 nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy. Biomed Res Int 2014;2014:814948.
24. Mi YJ, Liang YJ, Huang HB, et al. Apatinib (YN968D1) reverses multidrug resistance by inhibiting the efflux function of multiple ATP-binding cassette transporters. Cancer Res 2010;70:7981-91.
25. Zhang L, Zhang Y, Huang PY, et al. Phase II clinical study of gemcitabine in the treatment of patients with advanced nasopharyngeal carcinoma after the failure of platinum-based chemotherapy. Cancer Chemother Pharmacol 2008;61:33-8.
26. Chua D, Wei WI, Sham JS, et al. Capecitabine monotherapy for recurrent and metastatic nasopharyngeal cancer. Jpn J Clin Oncol 2008;38:244-9.
27. Hu S, He X, Dong M, et al. Efficacy and safety of gemcitabine combined with ifosfamide in patients with advanced nasopharyngeal carcinoma who failed platinum-based chemotherapy. Zhonghua Zhong Liu Za Zhi 2015;37:632-6.
28. Chen C, Wang FH, Wang ZQ, et al. Salvage gemcitabine-vinorelbine chemotherapy in patients with metastatic nasopharyngeal carcinoma pretreated with platinum-based chemotherapy. Oral Oncol 2012;48:1146-51.

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