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Anti-angiogenesis agents plus chemoradiotherapy for locally advanced nasopharyngeal carcinoma: A Systematic Review and Meta-analysis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 August 2023 and was last updated on 17 August 2023.

INTRODUCTION

Review question / Objective To evaluate the efficacy and safety of anti-angiogenesis agents plus chemoradiotherapy versus chemoradiotherapy in the treatment of locally advanced nasopharyngeal carcinoma.

Condition being studied Nasopharyngeal carcinoma(NPC), a malignant tumor originating from the epithelial cells of nasopharyngeal mucosa, is one of the most prevalent malignant tumors in head and neck. The distribution of NPC exhibits significant regional clustering, with more than 70% of new cases occurring in East and Southeast Asia. According to the International Agency for Research on Cancer, there were approximately 133000 new cases and around 80,000 deaths of nasopharyngeal carcinoma in 2020. Notably, the incidence and mortality are higher in males compared with females.

Nasopharyngeal carcinoma in early stage is primarily treated by radiotherapy. However, due to the lack of significant clinical symptoms in this stage, over 70% of patients have been in local advanced stage when diagnosed. According to the 2022 National Comprehensive Cancer Network(NCCN) guidelines, it is recommended that concurrent chemoradiotherapy(CRT) combined with adjuvant or induction chemotherapy be classified as Level 2A evidence for nasopharyngeal carcinoma in stage II-IVA. Currently, CRT is considered as the main treatment for locally advanced nasopharyngeal carcinoma(LANPC). Although the multidisciplinary treatment(MDT) model has effectively controlled local recurrence

rate, the rate of distant recurrence metastasis remains high. Therefore, it is urgent to explore a new cure to reduce the incidence of distant metastasis in patients with LANPC and further prolong the life of them.

The efficacy of antiangiogenic drugs has been demonstrated in various malignant tumors, such as non-small cell lung cancer, melanoma, colorectal cancer and so on. Studies have shown that anti-angiogenic therapy combined with radiotherapy can enhance the efficacy of treatment for tumor. Currently, CRT combined with antiangiogenic therapy has become popular in tumor research. A single-arm study RTOG0615 added angiogenesis inhibitor bevacizumab on the basis of standard treatment of LANPC with 2-year progression-free survival(PFS) of 74.7% and 2-year overall survival(OS) of 90.9%. A long-term update in 2020 revealed that the 5-year and 7-year PFS were respectively 61.2% and 56.3%, and the 5-year OS and 7-year OS were respectively 79.5% and 69.7%. The incidence of late grade 3 adverse events(AEs) was 36.4%, with no reported incidences of late grade 4 or 5 AEs. The result suggested that combined treatment therapy contributed to a higher survival rate without intolerable toxicity. On the contrary, some studies have found that the application of antiangiogenic drugs with CRT would not increase the complete response rate for nasopharyngeal tumors, providing no benefits in terms of OS and PFS for NPC patients.

Therefore, there is a controversy on whether combined treatment therapy, compared with CRT alone, can improve the efficacy of LANPC and whether it may increase adverse reactions. However, few relevant meta-analyses have been published. Thus, in order to provide new insights and evidence for the treatment of LANPC, we conducted this meta-analysis by reviewing randomized controlled trials(RCTs) and retrospective studies published in recent years to evaluate the efficacy and toxicity of anti-angiogenic drugs plus CRT.

METHODS

Participant or population Patients with locally advanced nasopharyngeal carcinoma confirmed by pathological diagnosis.

Intervention Anti-angiogenesis therapy combined with chemoradiotherapy.

Comparator Chemoradiotherapy alone.

Study designs to be included Randomized controlled trials and retrospective studies.

Eligibility criteria Inclusion criteria: (i). Research objects: Patients with locally advanced nasopharyngeal carcinoma confirmed by pathological diagnosis. (ii). Intervention measures: The experimental group was treated with anti-angiogenesis therapy combined with CRT, and the control group only used CRT. (iii). Outcomes and endpoints: The primary efficacy outcomes were complete response(CR), partial response(PR), progressive disease(PD), stable disease(SD), objective response rate(ORR) and disease control rate(DCR). The efficacy of two groups was evaluated according to the Response Evaluation Criteria in Solid Tumors. Complete response(CR): the disappearance of all target lesions. Partial response(PR): at least a 30% decrease from baseline in the sum of target lesion diameters. Progressive disease(PD): at least a 20% increase in the sum of target lesion diameters, using the smallest sum as a reference, and the absolute value of the sum of diameters increases by at least 5 mm, or the appearance of one or more new lesions. Stable disease(SD): The degree of reduction of target lesion did not reach PR and the degree of increase did not reach PD. ORR: the percentage of patients whose tumors shrinks to a certain extent and maintains for a certain time, including CR and PR cases. DCR: the percentage of patients whose tumors shrinks or stabilizes for a certain time, including CR, PR and SD cases. The secondary indicators were incidence of adverse reactions, including leukopenia, hepatotoxicity, nephrotoxicity, nausea and vomiting, hypertension and so on. (iv). Research type: All the trials included were randomized controlled trials or retrospective studies. Exclusion criteria: (i). Systematic reviews, editorials, animal experiments, case reports or single-arm trials. (ii). Duplicate articles, studies with irrelevant content or inconsistent outcomes, or studies with unreasonable trial designs. (iii). Clinical trials which is ongoing but no results available. (iv). Violation of any of the above inclusion criteria.

Information sources The relevant literatures from PubMed, Embase, Web of Science, The Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Chinese Biological Medicine (CBM), Wanfang, and VIP databases were systematically searched from the date of establishment to April 2023. Relevant clinical trials in the International Clinical Trial Registry Platform (ICTRP) and the Chinese Clinical Registry (ChiCTR) were also included. The following medical terms were included: Nasopharyngeal Neoplasms, Angiogenesis inhibitors, Endostar, Anlotinib, Apatinib, Bevacizumab, Sunitinib, Pazopanib, Chemoradiotherapy. Connecting each subject

word with its free word with the conjunction 'OR', and connecting each subject word with the conjunction 'AND'. The literature was strictly screened according to the inclusion and exclusion criteria, and finally the eligible literature was screened out.

Main outcome(s) The primary efficacy outcomes were complete response(CR), partial response(PR), progressive disease(PD), stable disease(SD), objective response rate(ORR) and disease control rate(DCR).

Quality assessment / Risk of bias analysis Randomized controlled trials(RCTs) and retrospective studies comprised our meta-analysis. We valued the quality of these studies by Cochrane Collaboration's tool and the Newcastle-Ottawa scale(NOS) respectively. The scoring standard of the Cochrane Collaboration's tool included the generation of random allocation sequence, concealment of allocation, blinding, integrity of outcome data, selective reporting and other sources of bias. The NOS mainly included selection(0–4 stars), comparability(0–2 stars), and outcome(0–3 stars). If studies' scores ≥ 6 stars, it would be regarded as high quality and enrolled in our meta-analysis.

Strategy of data synthesis All meta-analyses were conducted by Cochrane RevMan version 5.3 and Stata(version 17). All results were reported by risk ratios(RRs) and 95% confidence intervals(CIs) and presented in the form of forest plots. P-values were bilateral, $P < 0.05$ was considered statistically significant. We used the Cochrane Q test and I^2 statistic to evaluated the heterogeneity of all studies included. If $P > 0.1$ and $I^2 < 50\%$, the heterogeneity between studies was not significant, a fixed-effects model was used; otherwise, a random-effects model was used. Potential publication bias was assessed by funnel plots, Egger's tests, and Begg's tests.

Subgroup analysis None.

Sensitivity analysis Sensitivity analyses were performed in order to assess the influence of each study on overall outcome by way of excluding one study at a time.

Country(ies) involved China.

Keywords Anti-angiogenesis, chemoradiotherapy, nasopharyngeal carcinoma, neoplasms, meta-analysis.

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