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ORIGINAL ARTICLE

Combination treatment with antiEGFR monoclonal antibodies in advanced nasopharyngeal carcinoma : a meta-analysis

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Summary

Purpose: *The objective of this study was to compare the efficacy of the conventional treatment (radiotherapy/RT and chemotherapy/CT) and the combination treatment with antiepidermal growth factor receptor (anti EGFR) monoclonal antibodies in patients with primary nasopharyngeal cancer (NPC) using meta-analysis of data retrieved from the literature.*

Methods: *Seven databases (Pubmed, Embase, Cochrane Library, CBM, CNKI, Wanfang,VIP) were searched. Of 537 identified articles, 12 satisfied our eligibility criteria and entered this meta-analysis. A total of 821 patients in 12 randomized controlled clinical trials (RCTs) were included in the study to compare the effect in the short-term and long-term treatment.*

Results: *The combination treatment improved the objective complete remission rate (CR) of primary NPC and the metastatic lymph nodes, and the 1-year distant metastasis-free survival (MFS) rate relative risk (RR=1.40, 95%CI:1.29-1.53, p=0.00; RR=1.29, 95%CI:1.18-1.42, p=0.00; RR=1.17, 95%CI:1.01-1.35, p=0.03, respectively). There was no difference in the 2- and 3-year MFS rate (RR=1.06, 95%CI:0.85-1.33, p=0.60 ; RR=0.87, 95%CI:0.63-1.22) p=0.43, respectively).*

Conclusion: *The combination with anti EGFR monoclonal antibodies and conventional treatment (RT and/or CT) improved the short-term therapeutic effect, but this benefit disappeared after 1 year.*

Key words: *antiEGFR monoclonal antibodies, chemotherapy, nasopharyngeal neoplasms, radiotherapy*

Introduction

NPC is the most common malignant tumor in head and neck , mainly encountered in the Southeast Asia . According to reports, the annual incidence in this area ranges between 30-80/100,000 [1]. NPC has a tendency to metastasise to lymph nodes early, due to the abundant lymphatic network under the nasopharyngeal mucosa, and if RT isn't delivered timely, the recurrence rate of lymph nodes will be as high as 40% [2]. In recent years, combination of RT and CT is being used in the treatment of NPC, gradually becoming the best method for the treatment of patients with advanced NPC. But even so, the 5-year survival rate is only 40-50% [3,4]. With the development of biological treatments, molecular targeted therapies have become another main therapy for the treatment of malignant tumors. A study [1] found that EGFR is overexpressed in NPC patients, being an independent factor affecting prognosis. In addition, a meta-analysis of 1225 patients also confirmed that EGFR is a prognostic indicator in patients with NPC [5]. As the clinical use of antiEGFR monoclonal antibodies is continually increasing, a lot of NPC patients get benefits,but the actual therapeutic effects in the NPC patients are still controversial [6].

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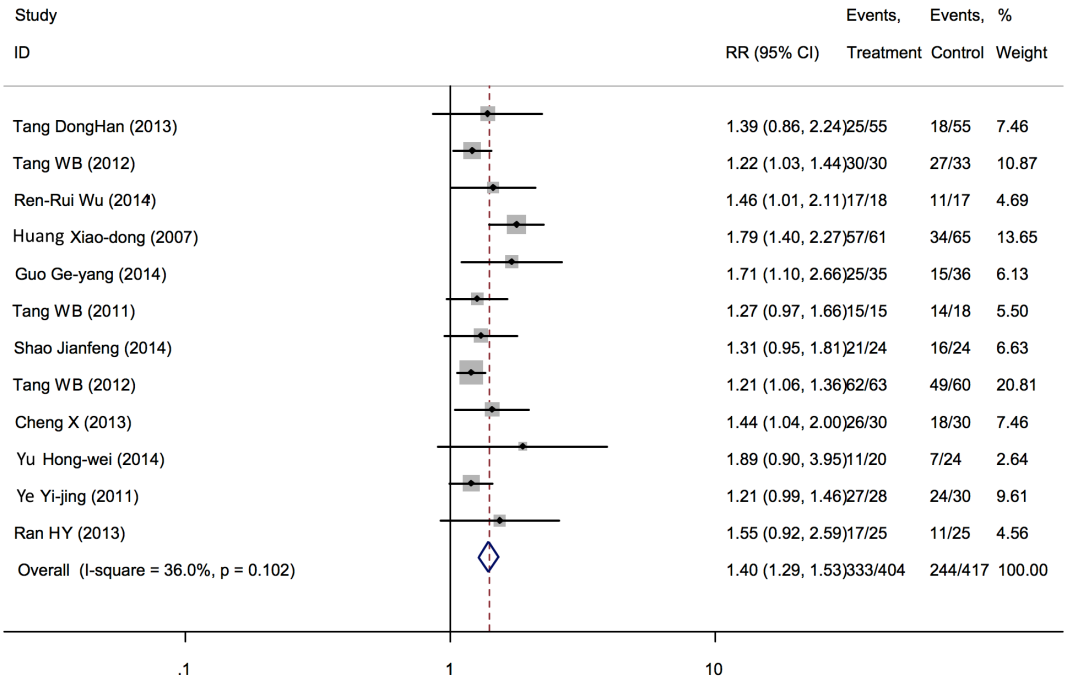

Figure 1. Forest plot for the meta-analysis of CR rate of the primary tumor.

Table 1. Basic information for the use of the antiEGFR monoclonal antibodies

Studies First author, (year), [ref. no.]	*Names of anti EGFR monoclonal antibodies*	*Doses*	*Cycles' repetitions (weeks)*
Tang DongHan (2013) [7]	Cetuximab	250 mg/m^2/week	4
Tang WB (2012) [8]	Nimotuzumab	100mg/week	7
Ren-Rui Wu (2014) [9]	h-R3	100mg/week	-
Huang Xiao-dong (2007) [10]	h-R3	100mg/week	-
Guo Ge-yang (2014) [11]	Nimotuzumab	100mg/week	6-7
Tang WB (2011) [12]	Nimotuzumab	100mg/week	6-7
Shao Jianfeng (2014) [13]	Nimotuzumab	100mg/week	7
Tang WB (2012) [14]	Nimotuzumab	100mg/week	6-7
Cheng X (2013) [15]	Nimotuzumab	100mg/week	7
Yu Hong-wei (2014) [16]	Nimotuzumab	100mg/week	7
Ye Yi-jing (2011) [17]	Cetuximab	400mg/m^2 first week,then 250mg/m^2 /week	7-8
Ran HY (2013) [18]	Cetuximab	400mg/m^2 first week,then 250mg/m^2 /week	7

In the present study we conducted a meta-analysis to evaluate the efficacy of the conventional treatment and the combination treatment with antiEGFR monoclonal antibodies in the treatment of NPC.

Methods

Bibliographic search

Search key words were: EGFR monoclonal antibody OR nimotuzumab OR cetuximab OR h-R3 OR c225) AND nasopharyngeal carcinoma. Seven databases (Pubmed, Embase, Cochrane Library, CBM, CNKI, Wanfang,VIP) were searched for entries until April 2015.

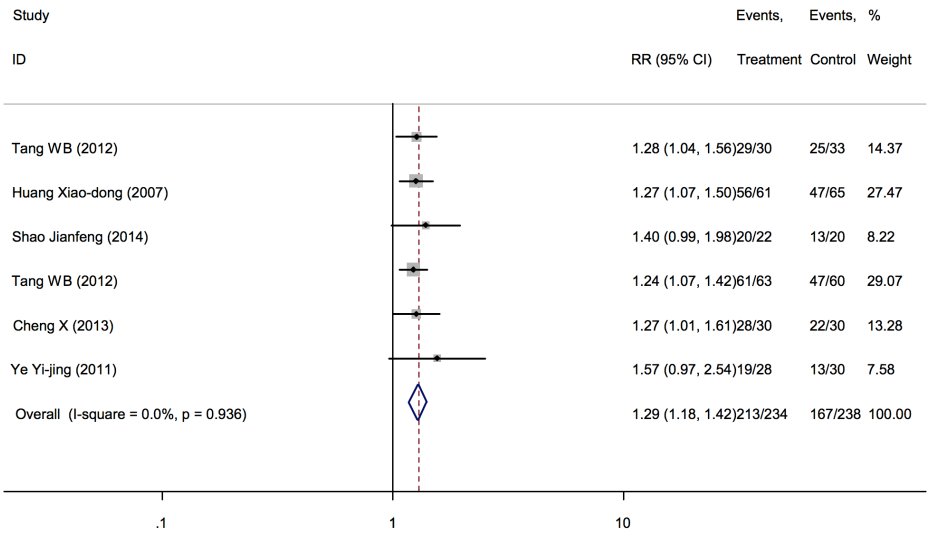

Figure 2. Forest plot for the meta-analysis of CR rate of metastatic lymph nodes

Inclusion criteria

Clinical trials that fulfilled the following criteria were included in the study: 1) Studies should be prospective randomized clinical controlled trials (RCTs) of NPC. 2) Comparisons of combined antiEGFR monoclonal antibodies with RT and or CT. 3) Patients should have advanced NPC diagnosed by pathological examination. 4) The end points of treatment in the short-term should be CR rate of the primary tumor and metastatic lymph nodes and in the long-term MFS rate in 1, 2 and 3 years. 5) Studies should be written in English or Chinese.

Quality evaluation of the studies

The evaluation of included studies was performed independently by 2 investigators (Cheng Yuan and Zhuo Chen). Disagreements were resolved through discussion with a third investigator (Xin-hua Xu). The quality was evaluated by the Jadad composite scale. A total of 12 studies [7-18] were included in the end. (Table 1).

Statistics

The statistical software (STATA12.0) was used in this meta-analysis. Pooled results were reported as relative risk (RR) and the corresponding 95% CI. Firstly, heterogeneity was identified thought the fixed-effect model. If heterogeneity was not significant ($p>0.1$, $I^2<50.0\%$), the fixed-effect model could be performed, otherwise, the random effects model was used. If patients dropped out or were lost, the short-term therapeutic effect was based on the per protocol analysis, and the long-term was based on the intention-to-treat analysis. The results of this meta-analysis were presented by forest plots, and a p value <0.05 was considered significant. Publication bias was evaluated though funnel plots, and then Egger's test was employed as quantitative indicator.

Results

CR rate of primary tumor

A total of 821 patients in 12 RCTs [7-18] were included to compare the CR rate of the primary tumor. The results of meta-analysis showed that CR rate of the primary tumor was higher with the combination treatment (RR=1.40, 95%CI:1.29-1.53, $p<0.001$) with no significant heterogeneity ($I^2=36.0\%$; Figure 1).

CR rate of metastatic lymph nodes

A total of 472 patients in 6 RCTs [8,10,13,14,17] were included to compare the CR rate of metastatic lymph nodes. Combined analysis showed that CR of the metastatic lymph nodes was higher with the combination treatment (RR=1.29, 95%CI:1.18-1.42, $p<0.001$) with no significant heterogeneity ($I^2=0.0$; Figure 2).

1-year MFS rate

A total of 315 patients in 4 RCTs [8,11,12,17] were included to compare 1-year MFS rate. The result of meta-analysis showed that 1-year MFS rate was higher in the combination treatment (RR=1.17, 95%CI:1.01-1.35, $p=0.03$) with no significant heterogeneity ($I^2=0\%$; Figure 3).

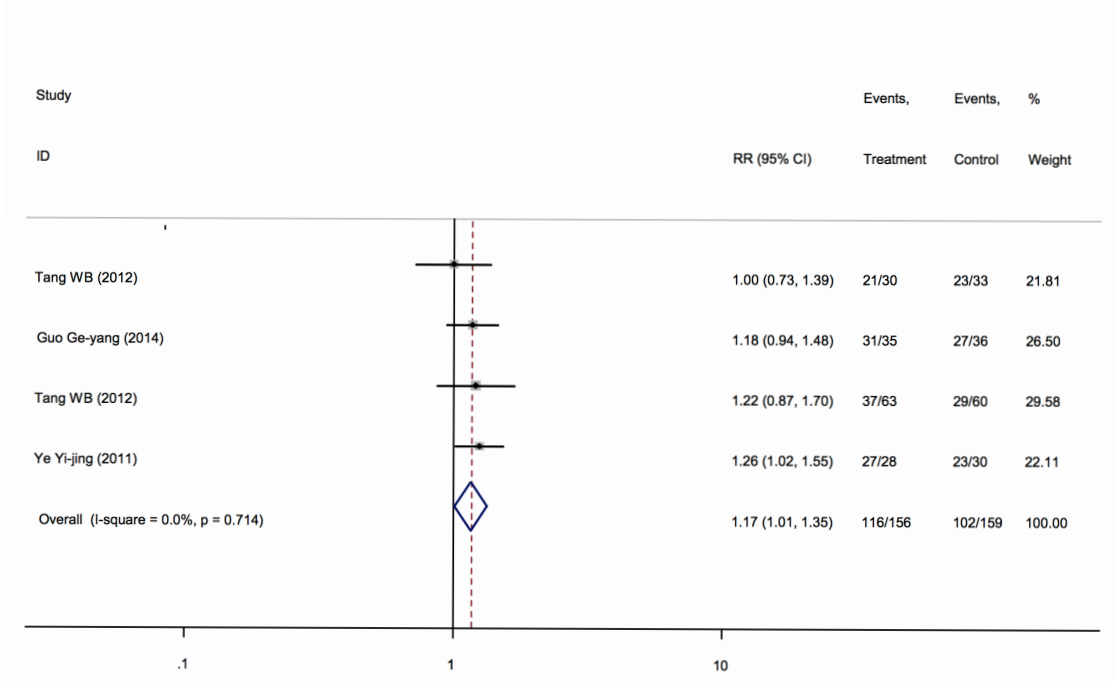

Figure 3. Forest plot of 1-year metastasis free survival rate.

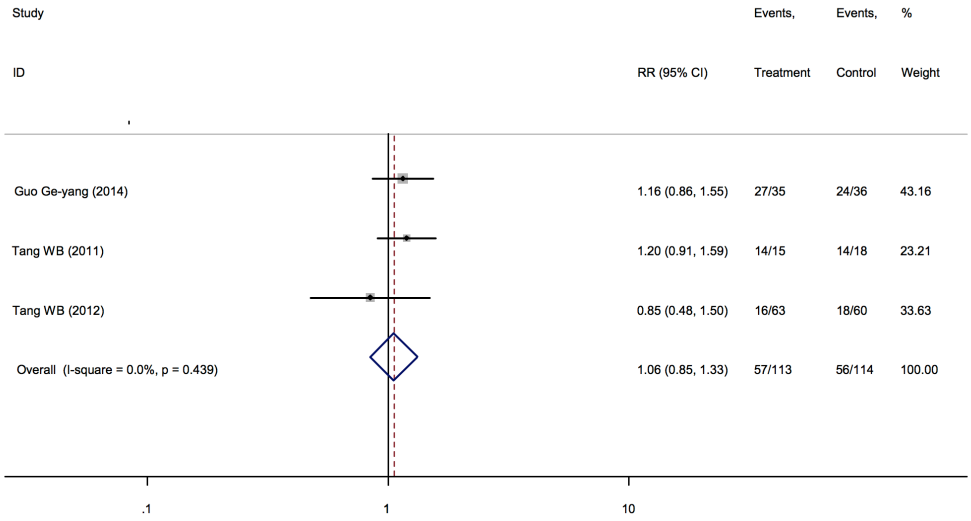

Figure 4. Forest plot of 2-year metastasis free survival rate.

2-year MFS rate

A total of 227 patients in 3 RCTs [11,12,14] were included to compare MFS in 2 years. The result of meta-analysis showed no significant difference between the 2 treatment groups (RR=1.06, 95%CI:0.85-1.33, p=0.60) with no significant heterogeneity (I^2=0%; Figure 4).

3-year MFS rate

A total of 158 patients in 2 RCTs [9,14] were included to compare MFS in 3 years. Similarly, the addition of antiEGFR showed not significant difference compared with conventional treatment (RR=0.87, 95%CI:0.63-1.22, p=0.43) with no significant heterogeneity (I^2=0%; Figure 5).

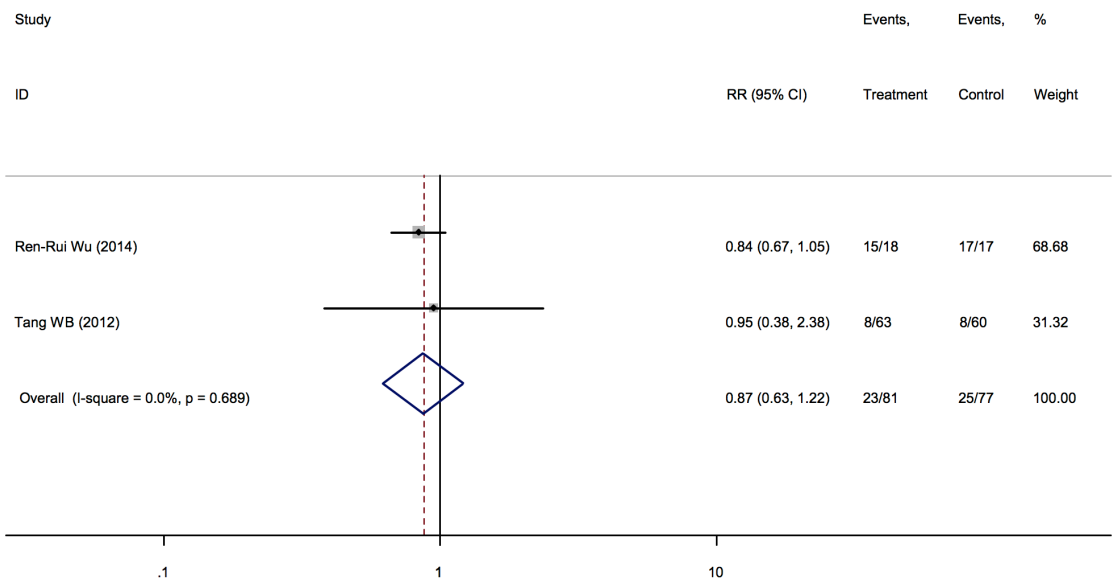

Figure 5. Forest plot of 3-year metastasis free survival rate.

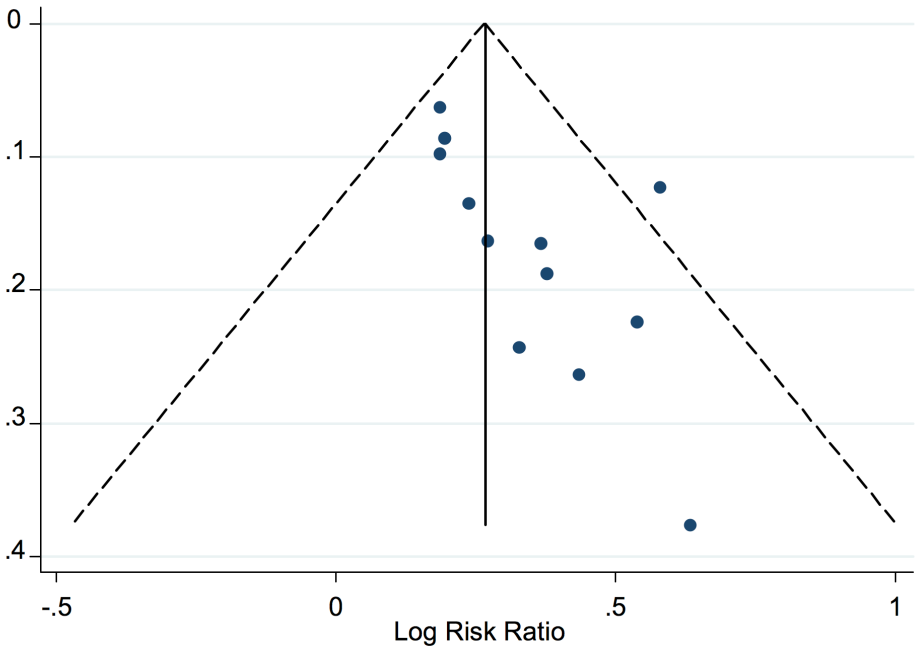

Figure 6. Funnel plot with pseudo 95% confidence interval of publication bias.

Publication bias

Funnel plots are shown in Figure 6. Arrangement of data points showed no evidence of obvious asymmetry. Formal evaluation using Egger's regression asymmetry test didn't show any evidence of publication bias (p=0.37, 95%CI: 0.17-0.42).

Discussion

AntiEGFR monoclonal antibodies provide new options of therapy for malignant tumors. Currently, the antiEGFR monoclonal antibodies have been widely used in the clinical treatment of a variety of malignant tumors, including lung cancer, colorectal cancer, breast cancer and other malignancies [19-21]. Due to the rather unsatisfactory results of conventional therapy for advanced NPC, antiEGFR monoclonal antibodies offer a new direction for the treatment of NPC [22].

This study aimed to assess the therapeutic effect of conventional therapy for advanced NPC combining antiEGFR monoclonal antibodies with conventional therapy. We found that patients who received combination treatment obtained significant improvement in CR rate of the primary tumor, CR rate of metastatic lymph nodes and 1-year MFS rate. The reasons may be that antiEGFR monoclonal antibodies can improve the sensitivity to RT and CT in the short-term. EGFR binding its downstream ligands (mainly EGF, TGF-α) can activate downstream signaling pathways, which leads to cell apoptosis and suppressed angiogenesis that are crucial for the growth and metastasis of solid tumors [23]. EGFR and its ligand (TGF-α) are overexpressed in nearly all head and neck tumors and *in vitro* tests inhibition of EGFR can enhance the radiosensitivity and has a synergistic effect with cytotoxic drugs to DNA damaging [23]. Studies have shown that after RT, the complex interactions between EGFR and DNA-protein kinase (PK) resulted in enhanced DNA-PK activity and DNA damage repair. Furthermore, inhibition of EGFR can make DNA-PK inactive, reduce DNA repair capacity and enhance the sensitivity of RT [24,25]. In addition, the mechanisms of action of antiEGFR monoclonal antibodies in the treatment of NPC may also involve circulating cancer stem cells (CSCs). Our research group made related research in the field of NPC CSCs, and confirmed the relationship between CSCs with certain characteristics and radiation sensitivity in NPC [26]. EGFR signaling pathway plays an important role in regulating NPC CSCs, and blocking EGFR signaling pathway in a NPC mice model through gefitinib has confirmed that this blocking can improve the therapeutic effect [27]. In nude mice experiments, cetuximab could obviously enhance the killing effect of local RT on NPC cells, and the mechanism involved increasing tumor differentiation and inhibition of tumor angiogenesis [28]. Cetuximab has demonstrated single-agent activity selectively in NPC cell lines CNE-2, C666-1, HONE-1 and HK1, with moderate to high EGFR protein expression. At the same time, cetuximab can enhance the antitumor effect of CT (cisplatin and paclitaxel) on NPC cells [29].

For long-term efficacy, the combination with antiEGFR monoclonal antibodies improved 1-year MFS rate, but this benefit disappeared in 2 and 3 years.This is consistent with a previous report [30], which showed that efficacy was not improved 1 year posttreatment due to resistance to antiEGFR monoclonal antibody. The mechanism of drug resistance mainly involves nuclear EGFR which participates in the process of cell proliferation and angiogenesis, and the antiEGFR monoclonal antibodies (e.g. cetuximab) promote the localization of EGFR in the nucleus, leading to drug resistance [30].

However, the limitations of this study cannot be ignored [1]. The results were limited by the quality of the included RCTs sample sizes, for example the samples sizes were not enough to give considerable power for the analyses, and the patients of RCTs were mainly Asians [2]. Only articles in English and Chinese were included,which might lead to potential publication bias, although publication bias was not significant in this study [3]. The results of statistics can not reflect the clinical reality completely because controls were not uniformely defined [4] and the results of this meta-analysis may be overestimated because of the heterogeneity, despite the fact that it was not significant in this study.

In conclusion, our study showed that antiEGFR monoclonal antibodies were necessary in the treatment of advanced NPC, considering the remarkable effect in CR rate of the primary tumor, CR rate of metastatic lymph nodes and 1-year MFS rate, although this benefit was lost in 2-and 3-year follow up.

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