RESEARCH ARTICLE

Editorial Process: Submission:02/04/2018 Acceptance:05/03/2018

Cetuximab or Nimotuzumab Versus Cisplatin Concurrent with Radiotherapy for Local-Regionally Advanced Nasopharyngeal Carcinoma: a Meta-analysis

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Abstract

Background: It is unclear whether Cetuximab (CTX) or Nimotuzumab (NTZ) concurrent with radiotherapy delivers equivalent or improved results with fewer toxicities over standard cisplatin (CDDP) concurrent with radiotherapy in locally advanced nasopharyngeal carcinoma (NPC). **Methods:** The strategy involved searching the PubMed, Embase, Cochrane Library, China National Knowledge Internet Web, Wanfang and Chinese Biomedical databases. Controlled clinical trials that compared concurrent CTX/NTZ with radiotherapy versus CDDP with radiotherapy in local-regionally advanced NPC were included. **Results:** In all, 1,239 patients in six clinical trials were included in the analysis. The hazard ratios (HRs) between the CTX/NTZ and CDDP groups were 1.01 (95% confidence interval (CI) 0.63-1.64), 1.06 (95% CI 0.50-2.25), 1.04 (95% CI 0.61-1.76), and 1.05 (95% CI 0.73-1.50) for overall survival, local-regional failure-free survival, distant metastasis failure-free survival, and disease-free survival, respectively. Significant differences were found in the incidences of grade 3-4 anaemia [Risk ratio (RR) 0.11 95% CI 0.02-0.58], grade 3-4 neutropenia (RR 0.23 95% CI 0.12- 0.44), grade 3-4 thrombocytopenia (RR 0.31 95% CI 0.12- 0.79), and grade 3-4 vomiting (RR 0.04 95% CI 0.00-0.29) in favour of the CTX/NTZ group. However, the patients in the CTX/NTZ group experienced a higher incidence of grade 3-4 skin rash (RR 6.45 95% CI 3.84-10.84). **Conclusions:** Regarding the efficacy and side effects, the combination of CTX / NTZ and radiotherapy may be an alterative treatment regimen of standard CDDP concurrent with radiotherapy in local-regionally advanced NPC, especially in patients who cannot tolerate or who refuse chemotherapy.

Keywords: Nasopharyngeal neoplasms- cetuximab- nimotuzumab- radiotherapy- meta-analysis

Asian Pac J Cancer Prev, **19 (5)**, 1397-1404

Introduction

The incidence rate of nasopharyngeal carcinoma (NPC) is high in Malaysia, Indonesia, Singapore, and south-eastern China (Torre et al., 2015). According to the National Comprehensive Cancer Network (version 1, 2017), a cisplatin (CDDP)-based concurrent chemoradiotherapy (CCRT) regimen is recommended as the standard treatment for local-regionally advanced NPC (category 2A). However, CDDP-based concurrent chemotherapy is often associated with high rates of grade 3-4 gastrointestinal and haematological toxicities that severely affect quality of life and medication compliance (Chan et al., 2002; Liao et al., 2016; You et al., 2017).

More than 80% of patients with NPC express the epidermal growth factor receptor (EGFR) (Taheri-Kadkhoda et al., 2009; Cao et al., 2012; Zhang et al., 2015). The addition of anti-EGFR monoclonal antibodies to radiotherapy (RT) improved survival in patients with local-regionally advanced squamous-cell carcinoma of the head and neck (SCCHN) (Bonner et al., 2006; Bonner et al., 2010). These findings prompted researchers to investigate whether replacing concurrent chemotherapy with anti-EGFR monoclonal antibodies to treat local-regionally advanced NPC is feasible and whether it would reduce treatment toxicity but not therapeutic effects.

Recently, several studies compared efficacy and safety between RT plus cetuximab (CTX) or nimotuzumab (NTZ) therapy and RT plus CDDP therapy in local-regionally advanced NPC (Xu et al., 2015; Li et al., 2016; Liao et al., 2016; Wu et al., 2016; You et al., 2017). You et al., (2017) retrospectively compared efficacy and safety between RT plus CTX/NTZ and RT plus CDDP in local-regionally

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advanced NPC. The two groups exhibited comparable rates of disease-free survival (DFS), local-regional failure-free survival (LRFS), distant metastasis failure-free survival (DMFS), and overall survival (OS). Nevertheless, in a trial conducted by Li et al., the 5-year OS and DFS rates were significantly lower in the NTZ group than in the CDDP group (Li et al., 2016). However, the sample sizes in these studies were small.

Thus, whether CTX/NTZ is an effective and safe alternative to CDDP is a compelling question for further studies. We therefore conducted a literature-based meta-analysis to investigate whether CTX/NTZ concurrent with RT achieves results that are equivalent to or better than those achieved by a standard CDDP concurrent with RT regimen in local-regionally advanced NPC. We also evaluated the incidences of toxicities.

Materials and Methods

Literature search strategy

The literature search was performed using the PubMed, Embase, Cochrane Library, China National Knowledge Internet Web (CNKI), Chinese Biomedical (CBM), and Wanfang databases. The search was performed using the following terms: nasopharyngeal carcinoma OR nasopharyngeal cancer OR nasopharyngeal tumour OR nasopharyngeal neoplasms, cetuximab OR nimotuzumab OR target, and radiotherapy. We searched for trials published and/or presented by 15 July 2017. In addition, the reference lists of the selected works were scanned to identify additional relevant articles. The Ethics Committee of the Affiliated Tumor Hospital of Guangxi Medical University approved this meta-analysis.

Inclusion and exclusion criteria

Trials were included if they met the following criteria: (1) the participating patients had local-regionally advanced NPC, (2) the studies compared CTX/NTZ and CDDP, and (3) the studies were controlled clinical trials, including RCTs, retrospective controlled trials or matched-pair analyses. However, the following were applied as exclusion criteria: (1) the study was not a controlled clinical trial; (2) the study was missing important information; and (3) the article was a review, letter, case report, meeting abstract, or trial protocol or comments. Eligible trials were independently identified by two reviewers, and discussions were resolved by a third person.

Quality assessment

The selected retrospective trials were evaluated and their results quantified using the 9-star Newcastle-Ottawa Scale (Wells et al., 2011). The quality of the RCTs was assessed using the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (Julian and Sally, 2011). The risk of bias in the RCTs was determined by scoring the following items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. The risk of bias was evaluated as high risk, low risk, or unclear according to these criteria. The quality of the included trials was independently assessed by two investigators. Any disagreements that arose during this procedure were resolved by consensus.

Data extraction

Information regarding the first author, study year, design type, inclusion period, number of patients in each of the CTX/NTZ and CDDP groups, clinical stage, regimen of RT, chemotherapy and target therapy was extracted from each study. Additionally, the primary and secondary end points, including the HRs of OS, LRFS, DMFS, DFS and haematological and non-haematological adverse events, were also extracted. If an HR and corresponding 95% confidence interval (CI) could not be obtained directly from the original trial, they were indirectly extracted from Kaplan-Meier curves as reported by Tierney et al. (Tierney et al., 2007).

Statistical analysis

OS, LRFS, DMFS, and DFS were calculated as HRs and 95% CIs to determine differences between the CTX/NTZ and CDDP groups. If HRs and 95% CIs could not be directly or indirectly obtained, risk ratios (RRs) and corresponding 95% CIs were calculated. Additionally, haematological and non-haematological adverse events were assessed as RRs with 95% CIs.

We evaluated the heterogeneity of the results using the I2 statistic to calculate inconsistency. An $I2 \geq 50\%$ indicated statistically significant heterogeneity. A fixed-effects model was applied if the heterogeneity test showed that there was no statistical significance ($I2 < 50\%$; $P > 0.1$). Otherwise, the following analyses were performed: (1) a sensitivity analysis was performed by excluding studies with potentially biased results; and (2) if statistically significant heterogeneity still existed, a random-effects model was used. All analyses were conducted using Stata version 12.0 software (StataCorp, College Station, Texas).

Results

Study selection and characteristics

Using the search criteria, we screened 2,334 records. Of these, 640 were duplicates. After we reviewed the titles and abstracts, 1,684 irrelevant publications were excluded. Additionally, four studies were excluded after the full text was reviewed. One study was a clinical trial with only a single arm (Niu et al., 2013). Another study included a control group that received only RT (Huang et al., 2007). In the study performed by Luo et al. (Luo et al., 2016), the concurrent chemotherapy regimen used in the control group was not CDDP. In the study conducted by Xia et al., the regimen used in the experimental group was a combination of CTX with chemoradiotherapy (Xia et al., 2017). Finally, 1,239 patients in six clinical controlled trials (Yin et al., 2014; Xu et al., 2015; Li et al., 2016; Liao et al., 2016; Wu et al., 2016; You et al., 2017) were included in the analysis., with 368 patients in the CTX/NTZ arm and 871 patients in the CDDP arm. A flow diagram demonstrating the process is shown in Figure 1.

Detailed information regarding the selected studies

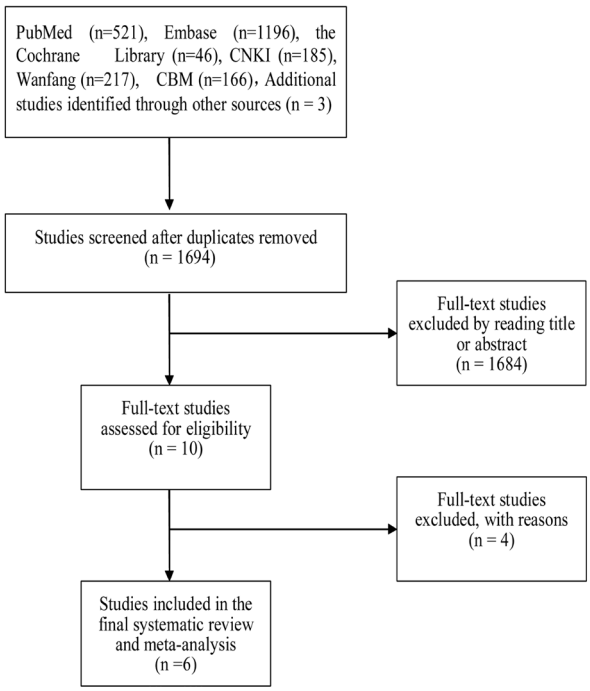

Figure 1. Selection Process for Clinical Controlled Trials Included in the Meta-analysis

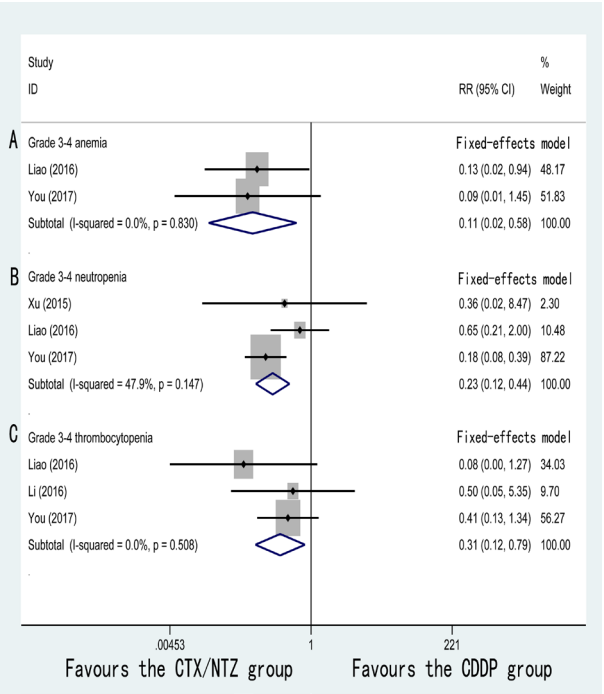

Figure 3. Forest Plots of the RRs for Grade 3-4 Anaemia, Neutropenia, and Thrombocytopenia in the CTX/NTZ Group and the CDDP Group

is provided in Table 1.

Quality assessment of the included studies

Of the six studies, four were retrospective controlled trials, and two were RCTs. The quality of the retrospective studies was determined according to the 9-star Newcastle-Ottawa Scale. All included studies were evaluated as high quality on this scale. In the two RCTs, random sequence generation, allocation concealment, and other biases were assessed as unclear (Xu et al., 2015; Liao et al., 2016). For the criteria related to selective reports, one study was considered high risk (Liao et al., 2016), and another study was considered low risk (Xu et al., 2015). Both of these trials were considered low risk for complete outcome data, blinding of participants and personnel, and blinding of outcome assessments (Xu et al., 2015; Liao et al., 2016).

Efficacy (Figure 2)

OS

Data regarding the OS were available in four trials involving 319 patients in the CTX/NTZ group and 816

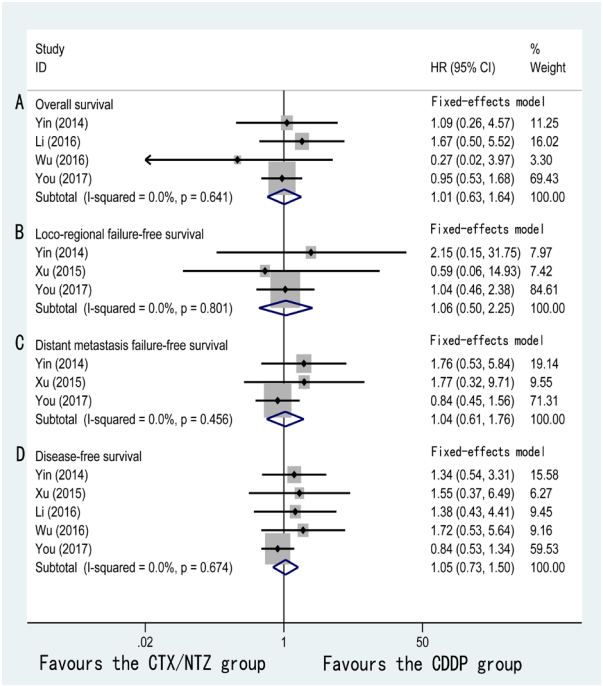

Figure 2. Forest Plots of the HRs for OS, LRFS, DMFS, and DFS in the CTX/NTZ Group and the CDDP Group

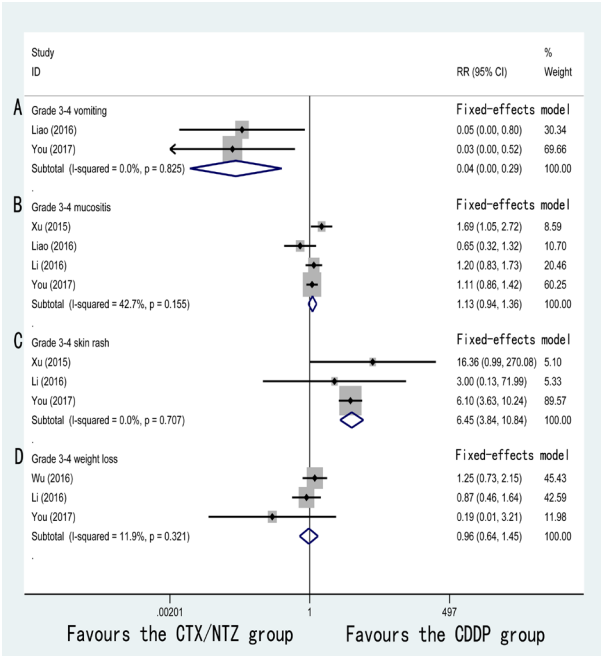

Figure 4. Forest Plots of the RRs for Grade 3-4 Vomiting, Mucositis, Skin Rash, and Weight Loss in the CTX/NTZ Group and the CDDP Group

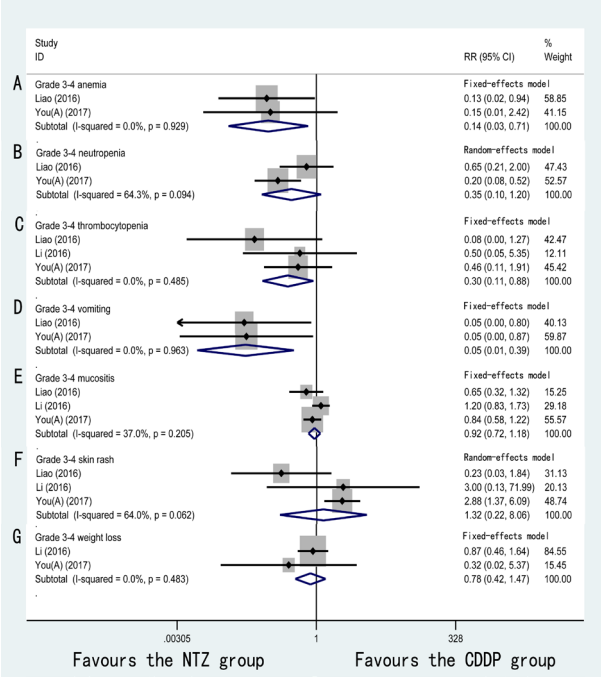

Figure 5. Forest Plots of the RRs for Grade 3-4 Anaemia, Neutropenia, Thrombocytopenia, Vomiting, Mucositis, Skin Rash, and Weight Loss in the NTZ Group and the CDDP Group

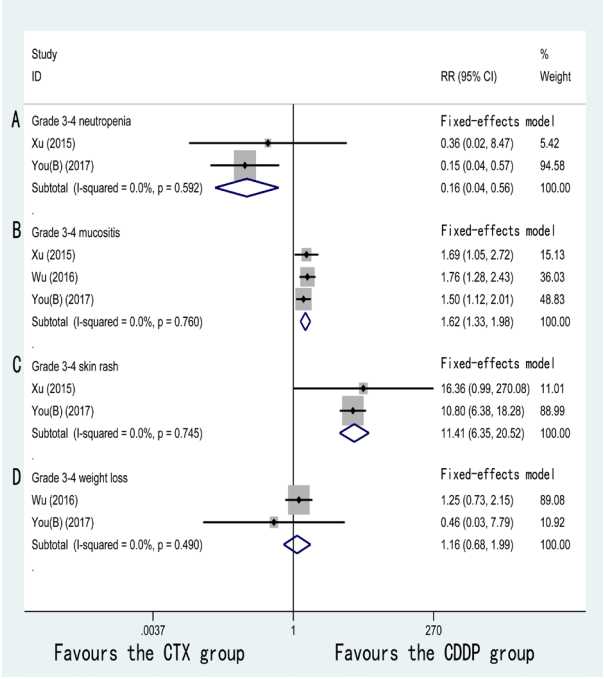

Figure 6. Forest Plots of the RRs for Grade 3-4 Neutropenia, Mucositis, Skin Rash, and Weight Loss in the CTX Group and the CDDP Group

patients in the CDDP group (Yin et al., 2014; Li et al., 2016; Wu et al., 2016; You et al., 2017). No significant heterogeneity was detected (I^2 = 0.0%, P = 0.641); and a fixed-effects model was therefore used. There was no significant difference in OS between the CTX/NTZ group and the CDDP group (HR 1.01, 95% CI 0.63 - 1.64). Data regarding 3-year OS were provided in two trials [11, 12]. These trials contributed 77 CTX group patients and 79 CDDP group patients. There was no significant difference in 3-year OS between the CTX group and the CDDP group (RR: 0.83 95% CI 0.25-2.79; heterogeneity: P = 0.561, I^2 = 0.0%).

LRFS

The pooled results (963 patients in 3 trials) (Yin et al., 2014; Xu et al., 2015; You et al., 2017) revealed that there was no significant difference in LRFS between the CTX/NTZ group and the CDDP group (HR: 1.06, 95% CI 0.50 – 2.25; heterogeneity: I^2 = 0.0%, P = 0.801).

DMFS

DMFS data were reported in three trials involving 232 patients in the CTX/NTZ group and 731 patients in the CDDP group (Yin et al., 2014; Xu et al., 2015; You et al., 2017). There was no significant difference in DMFS between the two groups (HR: 1.04, 95% CI 0.61-1.76; heterogeneity: I^2 = 0.0%, P = 0.456).

DFS

DFS data were available in five trials involving 340 CTX/NTZ group patients and 839 CDDP group patients (Yin et al., 2014; Xu et al., 2015; Li et al., 2016; Wu et al., 2016; You et al., 2017). There was no significant difference in DFS between the two groups (HR: 1.05, 95% CI 0.73-1.50; heterogeneity: I^2 = 0.0%, P = 0.674). A subgroup analysis showed that there was also no significant difference in DFS between the CTX group and the CDDP group (HR: 1.65, 95% CI -0.31-3.61; heterogeneity: I^2 = 0.0%, P = 0.935) [11, 12].

Toxicity

Grade 3-4 haematological toxicity

Two studies provided information regarding grade 3-4 anaemia (Liao et al., 2016; You et al., 2017), three studies provided information regarding grade 3-4 neutropenia (Xu et al., 2015; Liao et al., 2016; You et al., 2017), and three studies provided information regarding grade 3-4 thrombocytopenia (Li et al., 2016; Liao et al., 2016; You et al., 2017). Compared with the CDDP group, the CTX/NTZ group exhibited a lower risk of experiencing grade 3–4 toxic events, including anaemia (RR: 0.11, 95% CI 0.02-0.58; heterogeneity: P = 0.830, I^2 = 0%), neutropenia (RR: 0.23, 95% CI 0.12-0.44; heterogeneity: P = 0.147, I^2 = 47.9%), and thrombocytopenia (RR: 0.31 95% CI 0.12-0.79; heterogeneity: P = 0.508, I^2 = 0.0%) (Figure 3). A subgroup analysis showed that patients in the NTZ group had a lower risk of experiencing grade 3–4 toxic events, including anaemia (RR: 0.14, 95% CI 0.03-0.71; heterogeneity: P = 0.929, I^2 = 0%) and thrombocytopenia (RR: 0.30 95% CI 0.11-0.88; heterogeneity: P = 0.485, I^2 = 10.0%), but there was no significant difference in the incidence of grade 3-4 neutropenia (RR: 0.35, 95% CI 0.10-1.20; heterogeneity: P = 0.094, I^2 = 64.3%; random-effects model) (Figure 5). However, there was a lower risk of grade 3–4 toxic neutropenia in the CTX group than in the CDDP group (RR: 0.16, 95% CI 0.04-0.56; heterogeneity: P = 0.592, I^2 = 0.0%) (Figure 6).

Grade 3-4 vomiting

Two trials contributed information regarding

Table 1. Inclusion Criteria of Eligible Trials

Study	Design type	No. of patients (the CTX/NTZ group /the CDDP group)	Inclusion period	Stage	Radiotherapy	Induction Chemo-therapy	Concurrent Chemotherapy	Target therapy
CTX/NTZ + RT versus CDDP + RT								
Yin,2014	Retrospective	68 / 136	2008-2012	AJCC 7th edition II-IV B	IMRT: PGTV:69.96 - 73.92 Gy, PTV1:60.06 Gy, PTV2:50.96 Gy	none	CDDP	CTZ: 400mg/m^2 for the first week, then 250 mg/m^2/ week NTZ: 200 mg/week
IC + CTX/NTZ + RT versus IC + CDDP + RT								
Li,2016	Retrospective	52 / 52	2008-2013	AJCC 7th edition II-IV B	IMRT: 2.12–2.24 Gy/f/d, 5 f/week, to 70–74 Gy	TPF: DOC 75 mg/m^2, CDDP 25 mg/m^2/d d1-3, 5-Fu 600 mg/m^2 d1-5	CDDP 25mg/m^2/d d1-3, q3wks	NTZ: 200 mg/ week
Wu,2016	Retrospective	56 / 56	2008-2012	AJCC 7th edition II-IV B	IMRT: 2.12–2.24 Gy/f/d, 5 f/week, to 70–74 Gy	TPF: PTX 75 mg/m^2, CDDP 25 mg/m^2/d d1-3, 5-Fu 600 mg/m^2 d1-5	CDDP 25mg/m^2/d d1-3, q3wks	CTZ: 400mg/m^2 for the first week, then 250 mg/m^2/ week
You,2017	Retrospective	143 / 572 (the CTX group:58; the NTZ group: 85; the CDDP group: 572)	2009-2013	AJCC 7th edition II-IV B	IMRT: PGTVnx:66-70Gy/28-33f, PGTVnd:60-66 Gy/28-33f, PTV1:60 Gy/28-33f, PTV2:54 Gy/28-33f	PF:CDDP 80-100 mg/m^2 d1 + 5-Fu 800 mg/m^2 d1-5 TP: DOC 75 mg/m^2, CDDP 75 mg/m^2 d1 TPF: DOC 60 mg/m^2, CDDP 60 mg/m^2, 5-Fu 600 mg/m^2 d1-5	Cisplatin 100mg/m2 d1, q3wks	CTZ: 400mg/m^2 for the first week, then 250 mg/m^2/ week NTZ: 200 mg/week
Xu,2015	Prospective	21 / 23	2010-2011	AJCC 7th edition III-IV B	IMRT: PGTVnx:66-70.4Gy/30-32f, PGTVnd:66 Gy/30-32f, PTV1:60 Gy/30-32f, PTV2:54 Gy/30f	TP: DOC 75 mg/m^2, CDDP 80 mg/m^2 d1	CDDP 30 mg/m^2 d1, qwk	CTZ: 400mg/m^2 for the first week, then 250 mg/m^2/ week
Liao,2016	Prospective	28 / 32	2012-2013	AJCC 7th edition III-IV B	IMRT: PGTV:70 Gy, PTV1:61.25 Gy, PTV2:54 Gy	TPF: DOC 75 mg/m^2, CDDP 25 mg/m^2/d d1-3, 5-Fu 2500 mg/m^2 CIV 120h	CDDP 40mg/m^2 d1,qwk	NTZ: 200 mg/ week

CTX, Cetuximab; NTZ, Nimotuzumab; CDDP, Cisplatin; IC, Induction chemotherapy; RT, Radiotherapy; AJCC, American Joint Committee on Cancer; IMRT, Intensity modulated radiation therapy; DOC, Docetaxel; 5-Fu, 5-Fluorouracil; PTX, Paclitaxel; GTVnx, Gross target volume of the nasopharynx; GTVnd, Gross target volume of lymph node; PTV, Planning target volume

grade 3-4 vomiting in 171 patients in the CTX/NTZ group and 604 patients in the CDDP group (Liao et al., 2016; You et al., 2017). There were significantly fewer such events in the CTX/NTZ group (RR: 0.04, 95% CI 0.00-0.29, heterogeneity P = 0.825, I^2 = 0.0%) (Figure 4). A subgroup analysis showed that patients in the NTZ group were at lower risk than the CDDP group patients of experiencing grade 3–4 vomiting (RR: 0.05, 95% CI 0.01-0.39; heterogeneity: P = 0.963, I^2 = 0%) (Figure 5).

Grade 3-4 mucositis

Five trials contributed 1,035 patients for whom information was provided regarding grade 3-4 mucositis (Xu et al., 2015; Li et al., 2016; Liao et al., 2016; Wu et al., 2016; You et al., 2017). The risk of grade 3-4 mucositis was significantly higher in the CTX/NTZ group than in the CDDP group (RR: 1.24, 95% CI 1.05-1.45). However, significant heterogeneity was observed (heterogeneity: P = 0.04, I^2 = 61.0%). A sensitivity analysis resulted in the exclusion of one trial (Wu et al., 2016). Finally, a non-significant trend towards higher grade 3-4 mucositis was observed in the CTX/NTZ group (RR: 1.13, 95% CI 0.94-1.36; heterogeneity: P = 0.155, I^2 = 42.7%) (Figure 4). A subgroup analysis showed that patients in the CTX group had a higher risk than those in the CDDP group of experiencing grade 3-4 mucositis (RR: 1.62 95% CI 1.33-1.98; heterogeneity: P = 0.760, I^2 = 0.0%) (Figure 6), but there was no significant difference between the NTZ group and the CDDP group (RR: 0.92 95% CI 0.72-1.18; heterogeneity: P = 0.205, I^2 = 37.0%) (Figure 5).

Grade 3-4 skin rash

Four trials contributed information regarding grade 3-4 skin rash in 244 patients in the CTX/NTZ group and 679 patients in the CDDP group (Xu et al., 2015; Li et al., 2016; Liao et al., 2016; You et al., 2017), and there were significantly more such cases in the CDDP

group (RR 4.39 95% CI 2.80-6.87). However, significant heterogeneity was observed (heterogeneity: P = 0.02, I^2 = 70.0%). A sensitivity analysis resulted in the exclusion of one trial (Liao et al., 2016). Finally, we found that there was a significantly higher risk of this side-effect in the CTX/NTZ group (RR: 6.45, 95% CI 3.84-10.84; heterogeneity: P = 0.707, I^2 = 0.0%) (Figure 4). A subgroup analysis showed that patients in the CTX group were at higher risk than patients in the CDDP group of experiencing a grade 3-4 skin rash (RR: 11.41 95% CI 6.35-20.52; heterogeneity: P = 0.745, I^2 = 0.0%) (Figure 6), but there was no significant difference between the NTZ group and the CDDP group (RR: 1.32 95% CI 0.22-8.06; heterogeneity: P = 0.062, I^2 = 64.0%; random-effects model) (Figure 5).

Grade 3-4 weight loss

Three trials reported information regarding grade 3-4 weight loss for 251 patients in the CTX/NTZ group and 680 patients in the CDDP group (Li et al., 2016; Wu et al., 2016; You et al., 2017). The incidence of grade 3-4 weight loss was comparable between the two groups (RR: 0.96, 95% CI 0.64-1.45; heterogeneity: P = 0.321, I^2 = 11.9%) (Figure 4). A subgroup analysis showed that there was no significant difference between the CTX group and the CDDP group (RR: 1.16 95% CI 0.68-1.99; heterogeneity: P = 0.490, I^2 = 0.0%) or between the NTZ group and the CDDP group (RR: 0.78 95% CI 0.42-1.47; heterogeneity: P = 0.483, I^2 = 0.0%) (Figure 5 and Figure 6).

Discussion

To the best of our knowledge, this study is the first meta-analysis to compare the efficacy and toxicity of CTX/NTZ to those of CDDP concurrent with RT in local-regionally advanced NPC.

A combination therapy including anti-EGFR monoclonal antibodies and RT has been shown to improve survival in patients with local-regionally advanced HNSCC (Bonner et al., 2006; Curran et al., 2007; Bonner et al., 2010; Rodriguez et al., 2010). These reports have supported the notion that anti-EGFR monoclonal antibodies may also be used as an alternative to CDDP for definitive concurrent chemoradiotherapy in local-regionally advanced NPC. A randomized phase II study was conducted to evaluate the clinical efficacy and toxicity of induction chemotherapy followed by concomitant CDDP-chemoradiotherapy or CTX-RT in local-regionally advanced NPC (Xu et al., 2015). The results showed that the 3-year DFS, LRFS, DMFS, and OS rates were similar between the two groups. Nevertheless, Li et al., (2016) compared a NTZ group and a CDDP group and found that five-year OS and DFS were significantly higher in the CDDP group. It is therefore essential that prospective randomized controlled studies be performed to compare CTX/NTZ combined with RT to standard CCRT in local-regionally advanced NPC.

The overexpression of EGFR has been associated with an increased risk of both distant metastasis and radiation resistance (Cao et al., 2012; Sun et al., 2014). Hence, inhibiting EGFR may benefit affected patients by reducing the rate of distant metastasis and local-regional recurrence. In the present study, there was no significant difference in DMFS and LRFS between the CTX/NTZ group and the CDDP group. There are several potential explanations for this finding. First, the prognosis is worse in patients positive for EGFR expression than in those without (Cao et al., 2012; Sun et al., 2014). The rate of EGFR expression is high in NPC (Taheri-Kadkhoda et al., 2009; Zhang et al., 2015), and the improvements observed following treatment with CTX/NTZ might have been mitigated by the poorer prognosis reported in these patients. Second, several RCTs and meta-analyses have demonstrated that concurrent chemotherapy reduces the risk of both distant metastasis and local-regional recurrence in local-regionally advanced NPC (Lin et al., 2003; Lee et al., 2011; Blanchard et al., 2015; Yan et al., 2015). This reduced risk may have contributed to the negative results in the survival analysis. Moreover, induction chemotherapy has been demonstrated to improve both DMFS and LRFS (Song et al., 2015; Sun et al., 2016; Cao et al., 2017). Patients underwent induction therapy in five of the included trials, and the inclusion of these patients may have narrowed the effects of CTX/NTZ more than the effects of CDDP.

The present meta-analysis showed that fewer adverse events, including grade 3-4 anaemia, neutropenia, thrombocytopenia, and vomiting, occurred in the CTX/NTZ group. Therefore, to a certain degree, CTX/NTZ plus RT may be associated with better medication compliance among patients (Kong et al., 2015; Xu et al., 2015; Liao et al., 2016). However, the patients in the CTX/NTZ group, and especially those in the CTX group, experienced a higher rate of grade 3-4 skin rashes. Fortunately, these events are not severe enough to be life-threatening and are therefore less likely to result in the discontinuation of drug delivery (Bernier and Schneider, 2007; Curran et al., 2007). These side-effects frequently resolve after 3 months and do not cause long-term dysfunctions (Xu et al., 2015). Hence, CTX or NTZ may be an ideal alternative to CDDP in terms of adverse events.

There are several limitations to our meta-analysis. First, because all information was extracted from publications and we lacked access to individual patient data, it is possible that publication, reporting or selection bias may have occurred. Second, four of the included studies were retrospective trials in which the patients met specific selection criteria, and this may have resulted in selection bias. Third, some of the studies did not directly provide HRs and 95% CIs for OS, DFS, LRFS or DMFS. Two authors of the current study independently extracted the missing HRs from survival curves, and disagreements were resolved by a third person. However, errors may have occurred.

In conclusion, the efficacy of and side effects associated with CTX/NTZ combined with RT indicated that this treatment may be an alternative regimen to standard CDDP concurrent with RT in patients with local-regionally advanced NPC, especially in patients who cannot tolerate or who refuse chemotherapy.. However, the high rate of grade 3-4 skin rash should not be ignored. Therefore, multicentre, prospective, randomized controlled clinical

trials are needed to fully explore the usefulness of this treatment in this group of patients.

Conflict of interest

The authors declare they have no conflicts of interest.

Acknowlegements

This work was sponsored by grants from the National Natural Science Foundation of China (No. 81760544), Basic Ability Enhancement Project of Young Teachers in Guangxi Zhuang Autonomous Region (No. 2017KY0114), and the Youth Science Found of Guangxi Medical University (No. GXMUYSF201515).

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