A meta-analysis of cisplatin-based concurrent chemoradiotherapy with or without cetuximab for locoregionally advanced nasopharyngeal carcinoma

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Abstract

Background: It is unclear whether cetuximab (CTX) plus cisplatin-based concurrent chemoradiotherapy (CCRT) delivers equivalent or improved results over standard CCRT in locoregionally advanced nasopharyngeal carcinoma (NPC).

Methods: The strategy involved searching the PubMed, Embase, Cochrane Library, and Web of Science. Pooled hazard ratios (HRs) for overall survival (OS), distant metastasis-free survival (DMFS), locoregional relapse-free survival (LRFS), and disease-free survival (DFS), and pooled risk ratios for adverse events were meta-analyzed.

Results: In all, 1744 patients in 5 clinical trials were included in the analysis. Compared with CCRT group, CTX plus CCRT significantly improved DFS (HR = 0.59, 95% confidence interval [CI]: 0.41–0.86, P = .006) and distant metastasis failure-free survival (HR = 0.54, 95% CI: 0.38–0.76, P = .0004), rather than OS (HR = 0.70, 95% CI: 0.44–1.09, P = .12) and local-regional failure-free survival (HR = 0.82, 95% CI: 0.54–1.22, P = .33).

Conclusions: CTX plus CCRT might achieve higher DFS and DMFS with no significant difference in OS and LRFS. CTX plus CCRT group was associated with more grade 3–4 skin rash, mucositis and dermatitis. Large randomized trials were urgent to fully explore the usefulness of this treatment in the locally advanced NPC patients.

Abbreviations: CCRT = cisplatin-based concurrent chemoradiotherapy, CI = confidence interval, CTX = cetuximab, DFS = disease-free survival, DMFS = distant metastasis-free survival, EGFR = epidermal growth factor receptor, HR = hazard ratio, LRFS = locoregional relapse-free survival, NPC = nasopharyngeal carcinoma, NTZ = nimotuzumab, OS = overall survival, RR = risk ratio.

Keywords: cetuximab, concurrent chemoradiotherapy, locoregionally advanced nasopharyngeal carcinoma, meta-analysis, survival

1. Introduction

Nasopharyngeal carcinoma (NPC) is highly prevalent in Southeast Asia and Southern China, especially in the Guangdong province, where the incidence ranges from 20 to 30 per 100,000 population.[1–3] Most patients presented with locoregionally advanced NPC.[4] According to the 2017 National Comprehensive Cancer Network guidelines for head and neck cancer, concurrent platinum-based chemoradiotherapy (CCRT) is the present basic treatment for patients diagnosed with locoregionally advanced NPC.[5–12] Cisplatin-based chemotherapy combined with intensity-modulated radiotherapy had been the most commonly used treatment regimen for these stage II–IVb NPC patients. However, there was increasing evidence showing that CCRT alone might be inadequate for these patients who had a high potential for locoregional recurrence and distant metastasis.[13] For the patient who relapsed with locoregional recurrence and distant metastasis, the prognosis was poor with reported median survival of 8 months.[6,9] Therefore, new systemic strategies are urgently demanded for the treatment of NPC.

Previous study revealed the molecular target, epidermal growth factor receptor (EGFR), was highly expressed in more than 80% of locoregionally advanced NPC patients and correlated with poor clinical outcome.[14,15] Cetuximab (CTX), an anti-EGFR antibody, had been proven to improve survival of locoregionally advanced head and neck squamous cell carcinoma patients when combined with radiotherapy.[16] When radiation increased the expression of EGFR in NPC cells, inhibition of EGFR signaling made tumor cells more sensitive to radiotherapy.[17] Ma and his colleagues had shown a single-arm phase II clinical trial and reported that addition of CTX to concurrent
chemoradiotherapy for locoregionally advanced NPC was a feasible strategy. He and his colleagues had observed that combination of CTX and chemoradiotherapy was effective and tolerated. These findings prompted researchers to investigate whether patients of locoregionally advanced NPC could benefit from the concurrent combination of CTX plus chemoradiotherapy.

Recently, several studies compared efficacy and safety between CTX plus CCRT and CCRT alone in locally-advanced NPC. You and his colleagues retrospectively examined the benefits of CTX and CCRT compared with CCRT alone in patients with stage II–IVb NPC. The CTX plus CCRT group exhibited a significantly increased 3-year overall survival (OS), improved 3-year disease-free survival (DFS), and improved 3-year distant metastasis-free survival (DMFS). Nevertheless, in a clinical trial conducted by Lin et al, the 3-year OS, DFS, DMFS, and locoregional relapse-free survival (LRFS) rates of CTX with CCRT group were comparable to CCRT group. Several other studies also compared the efficacies and toxicities in both groups, but none of those were sufficient to demonstrate the prioritization of combination of CTX with CCRT.

However, there has been a debate over whether CTX with CCRT can achieve survival outcomes comparable to CCRT without additional toxicities. Therefore, we performed this literature-based meta-analysis to investigate the efficacy and safety of CTX plus CCRT and CCRT alone in locoregionally advanced NPC patients.

2. Materials and methods

This meta-analysis was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses guidelines and based on published studies with ethical approvals. No original clinical raw data was collected in this analysis, thus ethical approval was not necessary.

2.1. Search strategy

The literature search was performed using the Pubmed, Embase, Cochrane Library, and Web of Science (up to May 2018). The search was performed using the following terms: “nasopharyngeal carcinoma” OR “nasopharyngeal neoplasms” OR “nasopharyngeal cancer” OR “nasopharyngeal tumor,” “chemoradiotherapy” OR “concurrent CTX” OR “concurrent chemoradiotherapy” and “cetuximab”. All of the eligible articles were retrieved, and their references were checked for other relevant publications.

2.2. Inclusion and exclusion criteria

Trials should meet the following inclusion criteria:

1. The participating patients were local regionally advanced NPC, including stage II–IVb patients,
2. The patients were receiving cisplatin-based CCRT with or without CTX,
3. The studies were retrospective controlled trials or matched-pair analyses,
4. Randomized controlled trials will be considered for evaluation and maybe blinded or unblinded.

However, we excluded reviews, letters, case reports, meeting abstracts, trial protocols, comments, and animal experiments.

2.3. Quality assessment

The included retrospective trials were evaluated by 2 authors (BCW and LLS) and their results assessed using 9 star Newcastle–Ottawa scale. The Newcastle–Ottawa scale assesses trial quality by evaluating 3 domains: selection, comparability, and outcome for cohort studies or exposure for case-control studies. Selection and outcome or exposure domain that meets the criteria is given a star, while the comparability domain has a maximum of 2 stars. The maximum of stars is 9 points; scores 7 to 9 points were defined as high quality and scores < 7 as low quality studies.

2.4. Data extraction

Following information was extracted from each study: first author, publication year, study type, inclusion period, number of patients, staging information, median follow up, adjusting factors, adverse reactions, and survival events. When CTX and nimotuzumab (NTZ) were both studied in the same article, CTX data was extracted as much and separately as possible. If agreement could not be reached between the 2 authors (BCW and LLS), the third investigator (GP) was consulted to resolve the discrepancies.

2.5. Statistical analysis

Endpoints were determined as OS, DFS, LRFS, DMFS, and adverse effects. Time-to-event data from individual trials were assessed by hazard ratio (HR) and 95% confidence interval (CI). Additionally, hematological and nonhematological adverse events were calculated as risk ratios (RRs) with 95% CIs. All analyses were conducted using RevMan version 5.2 software (Cochrane Collaboration’s Information Management System). We evaluated the heterogeneity of the results using the forest plots, Chi-squared ($\chi^2$) tests, and I$^2$ statistic percentages. $P < .05$ was considered as significant outcomes. A fixed-effect model was applied if the heterogeneity test showed no statistical significance ($P > .10$, $I^2 \leq 50\%$), otherwise, a random-effect model was used.

3. Results

3.1. Study selection and identification

The preliminary literature screening yielded 98 records from the 4 databases, 90 records were excluded after screening their titles and abstracts. Of the remaining 8 potentially eligible studies, 3 were further excluded based on the exclusion criteria. Finally, 5 retrospective controlled studies of 1744 patients (411 in CTX + CCRT group and 1333 in CCRT group, respectively) were eligible for the meta-analysis published from 2000 to 2018. The flowchart of studies through the selection process was shown in Figure 1. The main characteristics of the 5 included studies are summarized in Table 1. According to the 9-srat Newcastle–Ottawa scale, 5 studies were classified as high quality studies (Table 2).

3.2. Effects of interventions

3.2.1. Survival events

3.2.1.1. Overall survival.

All selected studies were included in the OS analysis, including 411 patients in CTX + CCRT group and 1333 patients in CCRT group. Forest plot showed no difference of 3- and 5-year OS between the CTX with CCRT and
CCRT alone for NPC patient (3-year OS: HR = 0.65, 95% CI: 0.31–1.38, P = .26; 5-year OS: HR = 0.71, 95% CI: 0.40–1.25, P = .23) (Fig. 2A).

3.2.1.2. Disease-free survival. Data regarding the DFS were available in 2 trials involving 326 patients in the CTX + CCRT group and 963 patients in the CCRT group. No significant heterogeneity was detected (I² = 0.0%, P = .80), therefore, a fixed-effects was used. The risk of disease progression among the patients treated with CTX plus CCRT was lower compared with patients treated with CCRT alone (3-year DFS: HR = 0.59, 95% CI: 0.41–0.86, P = .006) (Fig. 2B).

3.2.1.3. Local-regional failure-free survival. Five studies were included in the LRFS analysis. There was no significant difference in the risk of locoregional relapse in the patients received CTX plus CCRT compared with patient received CCRT alone (3-year LRFS: HR = 0.76, 95% CI: 0.47–1.22, P = .26; 5-year LRFS: HR = 0.98, 95% CI: 0.45–2.13, P = .97) (Fig. 2C).

3.2.1.4. Distant metastasis failure-free survival. DMFS data were available in the 5 trials. Compared with CCRT alone, the addition of CTX to CCRT showed lower risk of distant metastasis (3-year DMFS: HR = 0.59, 95% CI: 0.39–0.90, P = .01; 5-year DMFS: HR = 0.44, 95% CI: 0.24–0.81, P = .008).

Figure 1. Study selection flow about the clinical controlled trials of concurrent chemoradiotherapy with or without cetuximab in patient with locoregionally advanced nasopharyngeal carcinoma.
3.3. Adverse events

Grade 3-4 adverse events were gathered from the enrolled studies, including hematological toxicities (anemia, neutropenia, thrombocytopenia, and leucopenia) and nonhematological toxicity, including skin rash, mucositis, dermatitis, nausea, vomiting, and weight loss.

3.3.1. Grade 3-4 hematological toxicities. Five enrolled studies provided the information regarding grade 3-4 anemia, neutropenia, thrombocytopenia, and leucopenia. There was no significant difference in hematological toxicities between CTX + CCRT group and CCRT group, including anemia (RR = 0.79, 95% CI: 0.39–1.62, P = .52), neutropenia (RR = 0.88, 95% CI: 0.40–1.93, P = .76), thrombocytopenia (RR = 0.70, 95% CI: 0.32–1.52, P = .36), and leucopenia (RR = 0.86, 95% CI: 0.57–1.29, P = .46) (Fig. 3).

3.3.2. Grade 3-4 skin rash. Two studies supplied data of grade 3-4 skin rash among which included 27 patients in the CTX + CCRT group and 171 patients in the CCRT group. Forest plot showed that addition of CTX to CCRT treatment significantly increased the risks of skin rash (RR = 3.80, 95% CI: 2.39–6.01, P = .0003). There was no heterogeneity for skin rash analysis (Fig. 2A).

3.3.3. Grade 3-4 mucositis. Five studies with 1744 patients reported the incidence of grade 3-4 mucositis. The addition of CTX to the CCRT significantly increased the risk of mucositis (RR = 2.75, 95% CI: 1.52–4.96, P = .0008) (Fig. 2B).

3.3.4. Grade 3-4 dermatitis. All eligible studies had the data for grade 3-4 dermatitis. Patients treated with CTX plus CCRT seemed to be more prone to occur dermatitis than those with CCRT alone (RR = 6.41, 95% CI: 1.90–21.62, P = .003) (Fig. 2C). There was no heterogeneity for dermatitis analysis (Fig. 2D).

3.3.5. Grade 3-4 gastrointestinal reactions. Two trials contributed information regarding grade 3-4 nausea in 178 patients in the CTX + CCRT group and 963 patients in the CCRT group, and there was no significant difference in the grade 3-4 nausea for both groups (RR = 1.10, 95% CI: 0.69–1.77, P = .69) (Fig. 2E). All enrolled trials contributed information regarding grade 3-4 vomiting, and forest plot showed no difference between CTX + CCRT group and CCRT group (RR = 1.31, 95% CI: 0.62–2.75, P = .48) (Fig. 2F).

There was no heterogeneity between studies for the DMFS analyses (Fig. 2D).
Figure 2. Forest plots and funnel plots of hazard ratios for 3-year and 5-year OS (A), DFS (B), LRFS (C), and DMFS (D) in patients between CTX + CCRT group and CCRT group. CI = confidence interval, CCRT = concurrent chemoradiotherapy, CTX = cetuximab, DFS = disease-free survival, DMFS = distant metastasis-free survival, $I^2$ = index of heterogeneity, LRFS = loco-regional relapse-free survival; OS = overall survival.
3.3.6. Weight loss. All 5 trials reported information regarding grade 3-4 weight loss. The CTX + CCRT group appeared similar risk of weight loss compared to CCRT group, with an RR $= 1.48$, 95% CI: 0.95–2.33, $P = .08$. There was no heterogeneity between studies for the weight loss analyses ($I^2 = 0\%$, $P = .57$) (Fig. 5C).

4. Discussion

To the best of our knowledge, this study is the first meta-analysis to directly compare CCRT and concomitant CTX and CCRT treatments in patients with locoregionally advanced NPC. Our results indicated that the combination of CTX and CCRT was associated with significant improved DFS and DMFS, rather than OS and LRFS in staged II-IVb NPC. Although NTZ included in the studies of You and Lin and induction chemotherapy conducted in the study of Lin might increase the heterogeneity, the 5-year survival analyses based on Li and Xia showed that CTX plus CCRT significantly prolonged DMFS, rather than OS and LRFS. Owing to the patients in our analysis were treated in China, these results mainly represented the efficacy and toxicities in the Asian population, especially in China.

A combination treatment including CTX plus radiotherapy had been shown to improve survival in NPC patients. 16,27,28 In studies comparing CTX plus radiotherapy with CCRT, the
primary interest was whether CTX could be used as an alternative to cisplatin-based CCRT in locoregionally advanced NPC. A retrospective analysis was conducted to examine the clinical efficacy and toxicity of the combination of CTX and CCRT compared with CCRT alone in patients with staged II-IVb NPC. The results showed that the treatment with CTX plus CCRT was associated with a significantly increased 3-year OS, DFS, and DMFS rates comparing with CCRT. Wu et al showed that CTX plus CCRT was associated with significantly improved 3-year LRFS in staged III-IVb patients and 3-year OS among patients with T4 and/or N3 category comparing with CCRT. Nevertheless, Li et al showed that adding CTX to CCRT did not significantly improve 5-year OS, LRFS, and DMFS, but exacerbate skin rash and mucositis. Therefore, multicenter prospective randomized clinical trials are needed to compared CTX plus CCRT with CCRT in locoregionally advanced NPC. Cunningham et al reported that CTX had clinical activity in overcoming resistance to previously administered chemotherapy. Moreover, Vermorken et al exhibited that combination of CTX with platinum-based chemotherapy (platinum-fluorouracil) significantly improved OS and PFS when given as first-line treatment in patients with recurrent or metastatic head and neck squamous cell carcinoma. Cao reported that positive expression EGFR had a significantly poorer 5-year OS and DFS than negative expression in patients with stage III-IVa NPC. Thus, we postulated that inhibition of EGFR might eradicate CCRT-resistant metastatic tumor cells. This could partially explain the significant increase in DFS and DMFS in CTX + CCRT group compared with CCRT group in the present study. In the present study, there was no significant difference in OS and LRFS between the CTX + CCRT group and CCRT group. However, considerably lower risk of death and tumor progression in OS and LRFS were observed. There are several potential explanation for this result. First, stage II/III patients were enrolled in the studies. In both studies conducted by Xu and Wu showed that CTX plus radiotherapy did not enhance OS rate compared with CCRT. Second, CCRT had achieved satisfactory locoregional control, thus, LRFS rates in both group had been narrowed. Moreover, patients with disease recurrence might be amenable to satisfactory salvage treatment such as re-irradiation, chemotherapy, and surgery, which might explain that the improvement in DFS and DMFS did not translate into an OS benefit. The present meta-analysis showed that skin rash, mucositis and dermatitis were the most serious adverse reactions. Patients with CTX plus CCRT experienced higher rates of grade 3-4 skin rash, mucositis and dermatitis.
rash, mucositis and dermatitis than those in CCRT alone group. In the phase II study, Ma et al reported that concurrent administration of CTX and chemoradiotherapy was a feasible regimen against locoregionally advanced NPC.[18] In the phase II multicenter study conducted by Baselga, they evaluated the toxicity of CTX plus CCRT in patients with recurrent or metastatic head and neck carcinoma and reported a well-tolerance in treatment-related toxicities.[36] These results indicated that the addition of CTX to CCRT could be considered when treating the patients with locoregionally advanced NPC.

There are several inherent limitations to our study. First, this meta-analysis included a small number of retrospective studies. Second, patients in the studies were all from China, and this may result in selection bias. Third, there was a significant heterogeneity in the subgroup analyses. Fourth, patients in the studies received different treatment modalities. Fifth, 2 studies used both CTX and NTZ.

In conclusion, this meta-analysis demonstrated that the combination of CTX with CCRT improved the DFS and DMFS compared with CCRT alone in patients with locoregionally advanced NPC. However, the high rates of grade 3-4 skin rash, mucositis, and dermatitis should not be ignored. These results indicated that CTX might be an alternative regimen to standard CCRT in patients with locoregionally advanced NPC. More prospective studies are needed to verify our findings.

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Figure 5. Forest plots and funnel plots of risk ratios for grade 3-4 nausea (A), vomiting (B), and weight loss (C) in CTX + CCRT group and CCRT group. CCRT = concurrent chemoradiotherapy, CTX = cetuximab.
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