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Beneficial effects of anti-EGFR agents, Cetuximab or Nimotuzumab, in combination with concurrent chemoradiotherapy in advanced nasopharyngeal carcinoma

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ABSTRACT

Objective: This study aimed to evaluate the efficacy and safety in locoregionally advanced nasopharyngeal carcinoma (NPC) patients receiving concurrent chemoradiotherapy (CCRT) plus Cetuximab (CTX) or Nimotuzumab (NTZ) compared to those receiving induction chemotherapy (IC) plus CCRT.

Materials and methods: From January 2008 to December 2013, 715 eligible patients were enrolled in the study. Using propensity scores to adjust for gender, age, Karnofsky performance status (KPS), tumor stage, node stage, and clinical stage, a well-balanced cohort was created by matching each patient who received CTX/NTZ plus CCRT (137 patients) with two patients who underwent IC plus CCRT (274 patients). The primary endpoint was overall survival (OS), and other outcome variables included disease-free survival (DFS), distant metastasis-free survival (DMFS) and loco-regional relapse-free survival (LRRFS).

Results and conclusion: The median follow-up was 57.0 months and 55.0 months for the CTX/NTZ plus CCRT group and IC plus CCRT group, respectively. No significant differences were found between the CTX/NTZ plus CCRT group and the IC plus CCRT group in 3-year OS (95.5% vs. 94.7%, P = 0.083), 3-year DFS (93.3% vs. 86.1%, P = 0.104), 3-year DMFS (96.2% vs. 92.5%, P = 0.243) and 3-year LRRFS (97.0% vs. 95.1%, P = 0.297). Patients undergoing IC plus CCRT suffered from severe hematologic toxicity and diarrhea compared with those treated with CTX/NTZ plus CCRT. The combination of CTX/NTZ with CCRT is comparable to IC plus CCRT treatment in survival outcomes for locoregionally advanced NPC patients but has a better safety profile than IC plus CCRT treatment.

Introduction

Nasopharyngeal carcinoma (NPC) is prevalent in southeast Asia and northern Africa, especially in southern China where the incidence can reach as high as 20/100,000 [1]. When newly diagnosed, most patients present with locoregionally advanced NPC [2]. According to the 2017 National Comprehensive Cancer network (NCCN) guidelines for head and neck cancer, concurrent chemoradiotherapy (CCRT) is recommended as basic treatment for stage II-IVb (AJCC/UICC 7th edition, 2011) NPC patients [3]. Compared to two-dimensional radiation therapy (2D-RT), intensity modulated radiation therapy (IMRT) achieved better local control rate up to 90%, with less radiation related toxicity [4–6]. However, distant metastasis remained the major cause of advannt fced NPC treatmeailure. To further improve distant metastasis-

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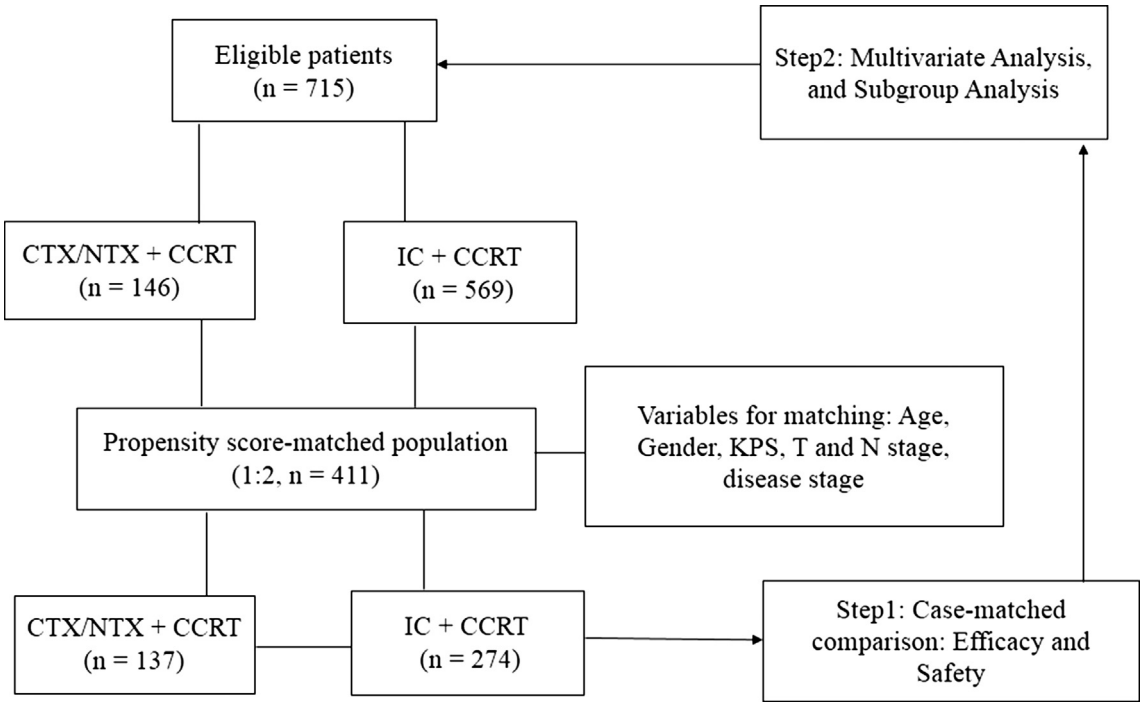

Fig. 1. CONSORT flow diagram.

free survival, many systemic treatment regimens were applied in locoregionally advanced NPC patients, such as induction chemotherapy (IC) combined with CCRT [7] and CCRT followed by adjuvant chemotherapy (AC) [8]. Recently, researchers reported that compared to CCRT alone, IC combined with CCRT could decrease the risk of progression failure, distant metastasis, and death in locoregionally advanced NPC [7,9,10]. However, patients receiving IC plus CCRT suffered from several adverse events, especially hematologic toxicity compared with those receiving CCRT alone, which led to cisplatin dose reduction when patients underwent concurrent chemoradiotherapy [7]. Therefore, new systemic strategies are urgently needed for the treatment of locoregionally advanced NPC.

The epidermal growth factor receptor (EGFR), a transmembrane glycoprotein, is a member of the epidermal growth factor family (EGF family). The activation of EGFR signal transduction pathway was involved in regulating cellular proliferation, apoptosis, angiogenesis and survival [11]. Overexpression of EGFR has been observed in many human cancers [12], and anti-EGFR agents are widely used in head and neck [13], non-small-cell lung [14], colorectal [15], and other cancers.

It has been reported that EGFR expression can be detected in nearly 90% nasopharyngeal carcinoma (NPC) patients and is associated with poor clinical outcomes [16]. Thus, systemic therapy combined with anti-EGFR agents, such as Cetuximab (CTX) and Nimotuzumab (NTZ), has become a novel promising treatment strategy for locoregionally advanced NPC [17–21]. Previously, our team reported that the efficacy of anti-EGFR agents plus IMRT in stage II-IVb (AJCC/UICC 7th edition, 2011) NPC patients was comparable to CCRT without additional intolerant adverse events [22]. Ma and his colleagues published a single-arm phase II study and reported that concurrent combination of Cetuximab, weekly cisplatin, and IMRT was a feasible treatment strategy for locoregionally advanced NPC [17].

Although the combination of IC with CCRT achieved improvement of PFS, DMFS and OS, it also caused severe hematologic toxicity, delay of radiation therapy, and dose reduction of concurrent cisplatin [7,10]. Our team conducted a retrospective study to directly compare anti-EGFR targeted therapy plus CCRT and CCRT alone and found that the addition of CTX/NTZ to CCRT could improve OS, disease-free survival (DFS), and DMFS with good tolerance [23]. However, a direct comparison between anti-EGFR agents plus CCRT and induction chemotherapy plus CCRT in locoregionally advanced NPC was lacking. In this study, we investigated whether the combination of anti-EGFR agents with CCRT could achieve survival outcomes comparable to IC plus CCRT without additional toxicities and examined its efficacy and safety in stage III to IVb NPC patients.

Patients and methods

Patients and study design

A retrospective study was conducted using the case records of patients with newly diagnosed NPC treated at the XXX Cancer Center from January 2008 to December 2013. The disease was restaged according to the International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) TNM classification (7th edition, 2011) based on clinical and radiography data. The pretreatment evaluation is presented in the Supplementary Appendix.

The inclusion criteria included the following: (a) histologically confirmed NPC; (b) disease classified as stage III-IVb (UICC/AJCC, 7th edition, 2011); (c) patients received IC plus CCRT or molecularly-targeted drug plus CCRT; (d) CCRT was cisplatin-based; (e) molecularly-targeted drug was CTX or NTZ with at least one cycle administered; (f) radiation technology was delivered by IMRT. The exclusion criteria were as follows: (a) the patient was diagnosed with a previous malignancy or other concomitant malignant disease; (b) the use of adjuvant chemotherapy.

Using propensity scores to adjust for age, gender, the Karnofsky performance status score (KPS), tumor stage (T stage) and node stage (N stage), and disease stage, we created a well-balanced cohort by matching each patient who underwent CTX/NTZ plus CCRT with two patients who underwent IC plus CCRT. We first conducted a case-matched comparison between the CTX/NTZ plus CCRT and IC plus CCRT arms regarding efficacy and safety. Subsequently, we conducted multivariate analysis and subgroup analysis based on all the eligible cases (Fig. 1). The clinical research ethics committee of XXX approved this study.