Oral Oncology 67 (2017) 167–174

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Combining cetuximab with chemoradiotherapy in patients with locally advanced nasopharyngeal carcinoma: A propensity score analysis

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ARTICLE INFO

Article history:
Received 25 September 2016
Received in revised form 14 February 2017
Accepted 22 February 2017
Available online 2 March 2017

Keywords:
Nasopharyngeal carcinoma
Cetuximab
Prognosis
Distant metastasis
Propensity score method

ABSTRACT

Objective: To compare the effectiveness of concurrent cisplatin chemoradiotherapy plus cetuximab with that of concurrent chemoradiotherapy (CCRT) alone in locoregionally advanced nasopharyngeal carcinoma (LRANPC) patients.

Materials and methods: A total of 3257 LRANPC patients from a prospectively maintained database were included in this observational study to examine the effectiveness of adding cetuximab to CCRT. We compared overall survival (OS), disease-free survival (DFS), locoregional recurrence-free survival (LRRFS), and distant metastasis-free survival (DMFS) using the propensity score method.

Results: In this cohort, 131 patients received CCRT plus cetuximab. Cetuximab-treated patients were more likely to receive intensity-modulated radiation therapy and were less likely to receive induction chemotherapy or adjuvant chemotherapy. The addition of cetuximab was associated with increased DMFS compared with CCRT alone based on univariable and multivariable analyses (5-year OS, 94.1% vs. 87.3%; $P = 0.044$), but not with increased OS, DFS, or LRRFS. Propensity score matching identified 96 patients in each cohort and confirmed that a DMFS benefit was associated with the addition of cetuximab (HR, 0.38; 95% CI, 0.15–0.99, $P = 0.044$). Subgroup analyses demonstrated a significant DMFS benefit with CCRT plus cetuximab in patients with N2-N3 stage disease compared with N2-N3 patients receiving CCRT alone (87.9% and 66.2%, respectively; $P = 0.045$).

Conclusions: In conclusion, the addition of cetuximab to first-line chemoradiotherapy is associated with an improvement in DMFS in patients with LRANPC. A prospective randomized clinical trial will be necessary to validate this result.

Introduction

Although radical radiotherapy (RT) is potentially curative for patients with locoregionally advanced nasopharyngeal carcinoma (LRANPC), treating patients with LRANPC remains a challenge [1]. Since the introduction of intensity-modulated radiation therapy (IMRT), excellent locoregional control has been reported by single institutions and in multi-institutional settings, but distant metastasis has remained the main cause of treatment failure [2–5]. Several randomized trials and meta-analyses have demonstrated a survival advantage with the use of concurrent cisplatin-based chemoradiotherapy, but approximately 30% of patients who receive this regimen experience treatment failure (especially if they develop distant metastasis) and ultimately succumb to their disease [6,7]. Therefore, more effective systemic treatments are needed to further reduce the development of distant metastasis in patients with LRANPC.

Cetuximab is a chimeric human-murine immunoglobulin G1 monoclonal antibody that selectively binds to the epidermal growth factor receptor (EGFR) with high affinity [8]. Because more than 80% of patients with nasopharyngeal carcinoma (NPC) express the EGFR and given the important role of the EGFR pathway in the development of NPC, the combination of cetuximab with

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http://dx.doi.org/10.1016/j.oraloncology.2017.02.026
1368-8375/

chemoradiotherapy could theoretically improve the outcomes of NPC patients [9–11]. Nevertheless, reports about using cetuximab in the treatment of LRANPC are rare. Several single-arm studies have investigated the effectiveness and toxicity of integrating cetuximab into chemoradiation for the treatment of LRANPC patients, and the regimen was effective and well tolerated in these studies [12–15]. Findings from a matched case-control study and a phase 2 prospective study have shown that cetuximab concurrent with RT was associated with a similar efficacy as standard cisplatin concurrent with IMRT but was also associated with increased rates of mucositis [16,17]. However, a prospectively randomized clinical trial regarding cetuximab in combination with chemoradiotherapy compared with chemoradiotherapy alone in patients with LRANPC has not been reported to date, so the treatment efficacy of cetuximab combined with routine chemoradiotherapy for the treatment of NPC patients with locoregionally advanced disease is unclear.

A significant breakthrough for patients with locally advanced head and neck cancer (LAHNC) was achieved in 2006 with a pivotal trial. This trial demonstrated that a 10% overall survival (OS) benefit when cetuximab was added to RT for the treatment of LAHNC. Based on these encouraging results, at the Sun Yat-Sen University Cancer Center (SYSUCC), which is one of the largest centers for NPC treatment and which is located in an NPC-endemic area [18], cetuximab concurrent with chemoradiotherapy has become a selective treatment for LRANPC patients since 2006. Therefore, we conducted the present observational study to examine the effectiveness of concurrent cisplatin chemoradiotherapy plus cetuximab compared with concurrent chemoradiotherapy (CCRT) alone for the treatment of patients with LRANPC.

Patients and methods

Patient selection

This study was reviewed and approved by the institutional review board and ethics committee of the SYSUCC (GZR2013-086). Written informed consent for treatment was obtained from all patients.

The records of patients newly diagnosed with NPC at the SYSUCC between January 1st, 2006, and June 1st, 2013, were identified from a prospectively created database. The inclusion and exclusion criteria are summarized in Fig. 1. Patients were excluded if they had stage I-II disease, distant metastatic disease, or missing medical data; died during the RT period; or had not received CCRT. Additional information, including patient demographics, pathological diagnosis, imaging diagnosis, TNM stage, smoking history, chemotherapy pattern, radiation technology and dosage, and follow-up, was collected from electronic and paper medical records.

Treatment

Induction or adjuvant chemotherapy (IC/AC), which was cisplatin-based chemotherapy, i.e., cisplatin in combination with fluorouracil or with taxane and fluorouracil, was administered every three weeks for two or three cycles. Concurrent chemotherapy consisted of cisplatin and was either given weekly or on weeks 1, 4, and 7 of RT. In terms of cisplatin dosing schedules either 30–40 mg/ m^2 once a week or 80–100 mg/m^2 every 3 weeks is accepted practice. For the patients received cetuximab treatment, cetuximab was administered at a loading dose of 400 mg/m^2 one week prior to the RT, followed by weekly doses of 250 mg/m^2. Of these patients, 1498 were treated with conventional two-dimensional (2D-CRT) or three-dimensional (3D-CRT) conformal RT, and 1759 were treated with IMRT, accounting for the whole cohort. RT quality assurance (QA) was performed before radiation treatment for all the NPC patients. The details of the RT techniques used at the SYSUCC were described in previous studies [19,20].

Variables

We considered patient-, tumor-, and treatment-based variables in the analysis. The patient-based variables included age, sex, education, smoking status, and drinking status. The tumor-based variables included World Health Organization (WHO) pathology, T stage, and N stage classifications. The T stage and N stage were re-categorized according to the American Joint Committee on Cancer classification system, 7th edition, by XY, XW and LH. The treatment-based variables included radiation type and chemotherapy pattern. Radiation type was dichotomized as either

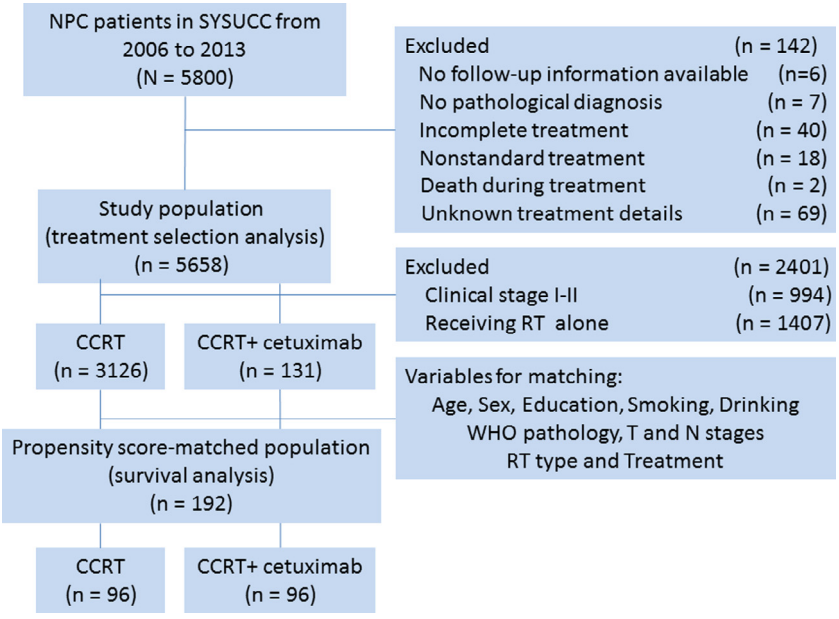

Fig. 1. Diagram of the analytic cohort for survival analysis. Abbreviations: NPC, nasopharyngeal carcinoma; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; SYSUCC, Sun Yat-Sen University Cancer Center; WHO, World Health Organization.