
1) Goshi Nishimura, 2) Hiromitsu Hatakeyama, 3) Osamu Shiono, 4) Masataka Taguri, 2) Masanori Komatsu, 1) Daisuke Sano, 2) Naoko Sakuma, 1) Kenichiro Yabuki, 1) Yasuhiro Arai, 2) Kunihiko Shibata, 1) Yoshihiro Chiba, 1) Teruhiko Tanabe, 1) Nobuhiko Oridate

1) Department of Otorhinolaryngology, Head and Neck Surgery, Yokohama City University, School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan

2) Department of Otorhinolaryngology, Yokohama City University Medical Center, 4-57 Urafune-cho, Minami-ku, Yokohama 232-0024, Japan

3) Department of Otorhinolaryngology, Yokohama Rosai Hospital, 3211 Kodukue-cho, Kohoku-ku, Yokohama 222-0036, Japan

4) Department of Data Science, Yokohama City University, School of Data Science, 2-22 Seto, Kanazawa-ku, Yokohama 236-0027, Japan
Correspondence to: Goshi Nishimura, Department of Otorhinolaryngology, Head and Neck Surgery, Yokohama City University School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama, 236-0004, Japan. Tel: +81-45-787-2687, E-mail: gnishimu@yokohama-cu.ac.jp

ABSTRACT

Background: We confirmed the safety of postoperative bio-chemoradiotherapy (B-CRT) using cetuximab (Cmab) and docetaxel (DTX) in a small number of patients with cis-platinum (CDDP)-intolerant core high-risk head and neck cancer.

Objective: To assess treatment efficacy, we planned a phase II study of postoperative B-CRT for patients with CDDP-intolerant core high-risk head and neck cancer and compare the results to those of previously collected radiotherapy data.

Methods: Patients who underwent definitive surgery for nasal/paranasal, oral cavity, laryngeal, oropharyngeal, or hypopharyngeal advanced cancer; whose postoperative pathological results indicated core high risk for the recurrence, e.g., positive margin in the primary site and/or extranodal extension; and who were CDDP intolerant will undergo postoperative B-CRT. The primary endpoint is
2-year disease-free survival (DFS).

**Results:** The expected 2-year DFS is set at 55%, and the calculated sample size is 35 patients, according to a statistical analysis that was based on previous reports.

**Conclusions:** This treatment method is expected to improve the survival rate of patients with severe head and neck cancer.

**Trial registration:** UMIN Clinical Trials Registry: UMIN000031835. Registered on March 22, 2018.

**Key words:** Core high-risk head and neck cancer, postoperative biochemoradiotherapy, cetuximab, docetaxel, cis-platinum intolerant

**BACKGROUND**

Most patients with head and neck cancers present with advanced disease stages during their first hospital visit. For patients with advanced head and neck cancers, surgery is a common definitive therapy. After surgery, a pathological evaluation is necessary to decide upon additional therapy. The pathological risk factors for recurrence and/or distant metastases after surgery are as follows: positive surgical margins, T3 and T4 pathologies, positive perineural invasions
and/or vascular tumor embolism of the primary site, and extranodal extension (ENE) and/or multiple positive metastasis to lymph nodes. Patients with these results are recommended to undergo postoperative radiotherapy. Among these risk factors, microscopically involved surgical margins of the primary site and/or ENE is considered to be core high-risk factors that indicate a poor prognosis. The outcome for patients with these core high-risk factors could be improved by concurrent chemotherapy during postoperative radiotherapy.

The standard protocol for postoperative chemoradiotherapy is the concurrent use of cis-platinum (CDDP; 100 mg/m² once every 3 weeks) during radiotherapy (total dose of 66 Gy) for patients with core high-risk factors. However, many of these patients are intolerant to CDDP due to advanced age, poor renal function, hearing impairment and/or poor general condition. One option to overcome these problems is the combined administration of cetuximab (Cmab) and docetaxel (DTX) during postoperative radiotherapy. This regimen has been shown to afford favorable outcomes, with improved disease-free survival (DFS) and overall survival (OS) and less toxicity compared to high-dose CDDP administration. A phase II/III trial (RTOG 1216) of this regimen is ongoing. Focusing on the reduced toxicity of this regimen, we administered the
combination of Cmab and DTX during postoperative radiotherapy for a limited number of patients with CDDP-intolerant core high-risk head and neck cancer and established the safety of this procedure. Here, we propose a multicenter, single-arm phase II trial to confirm the efficacy of postoperative biochemoradiotherapy (B-CRT) using Cmab and DTX for patients with CDDP-intolerant core high-risk head and neck cancer (Fig. 1).

**METHODS/DESIGN**

**Study setting**
Multicenter single-arm open-label nonrandomized trial.

**Endpoints**
The primary endpoint is 2-year DFS, and the events are uncontrollability of existing cancer (locoregional remnant, locoregional recurrence, and/or distant metastasis), appearance of new primary cancer, and death. The secondary endpoints are 2-year OS, 2-year recurrence-free survival (RFS), and 2-year locoregional control survival (LCS). The event of OS is death, events of RFS are locoregional recurrence and distant metastasis of existing cancer and death, and events of LCS are locoregional recurrence and death. In patients with
locoregional recurrences of advanced head and neck cancer, 60-70% of these recurrences become apparent within 1 year after the initial treatment, and 90-100% become apparent within 2 years \(^6,^7\). Accordingly, the endpoint is set at 2 years.

**Eligibility criteria**

Head and neck cancer is classified according to the 8\(^{th}\) edition of the TNM classification system \(^8\). Patients with clinical advanced stage (stage III/IV) nasal/paranasal sinus, oral cavity, laryngeal, oropharyngeal, and hypopharyngeal carcinoma, which are considered resectable by definitive surgery, are the first candidates. Among the first candidates, patients with a postoperative pathological evaluation that reveal a microscopically involved surgical margin of the primary site and/or ENE are the second candidates. Among the second candidates, patients defined as CDDP intolerant are enrolled.

**Inclusion criteria**

Prior to enrollment in this trial, the patients must meet all of the following criteria: pathologically proven carcinoma; primary tumor located in the nasal/paranasal sinus, oral cavity, larynx, oropharynx, or hypopharynx; clinically
advanced stage (stage III or IV) on visual, endoscopic examinations, imaging examinations, e.g., computed tomography (CT), magnetic resonance imaging (MRI), ultrasonic echo (US), and/or positron-emission tomography (PET)-CT; primary site assessed as resectable by definitive surgery and regional lymph node assessment by neck dissection on CT, MRI, and/or US; no distant metastasis on PET-CT (cM0); age over 20 years (regarded as a legal adult in Japan); performance score (PS) 0-2 on Eastern Cooperative Oncology Group (ECOG) criteria; sufficient general condition for operation under general anesthesia; CDDP intolerant; e.g., advanced age (over 75 years), poor renal function (estimated glomerular filtration rate [e-GFR] < 60 ml/min/1.73 m²), insufficient bone marrow function (white blood cell count, <3,000/mm³; neutrophil count, <1,500/mm³; platelet count, <7.5 X10⁴/mm³), hearing impairment, drug allergy, past history of CDDP use, and/or poor general condition; and provision of written informed consent.

Exclusion criteria
Prior to enrollment in this trial, the patients must not meet any of the following criteria: incurable synchronous malignancies, priority systemic diseases, and
refusal to undergo definitive surgery and/or postoperative radiotherapy.

**Enrollment**

Patient enrollment started on April 1, 2018, and the scheduled period is 3 years.

**Treatment methods**

**Surgery**

Definitive primary resection is performed for the primary site, with simultaneous neck dissection for node-positive cases.

**B-CRT**

Radiotherapy is administered in conventional fractions of 1.8 Gy for a total dose of 66.6 Gy, 5 days per week, using 4-6 MV X-rays. The radiation fields are set up for the primary tumor and prophylactically, the bilateral cervical lymph node area (levels I-V and the retropharyngeal lymph node area). The cervical lymph node area is administered prophylactic doses of 45 Gy, with lateral opposed fields to the upper and anterior lower neck. The B-CRT regimen consists of weekly Cmab (week 1: 400mg/m²; subsequent weeks: 250 mg/m²) and weekly DTX (25mg/m²). Cmab is discontinued for grade 3-4 hypersensitivity, and DTX is discontinued for grade 4 hyperinsensitivity. Termination or suspension of Cmab
administration, DTX administration, and/or radiotherapy is considered based on grade 3-4 adverse events and/or patient status.

Adverse event evaluation

Adverse events are scored according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 4.0. Patients are assessed once or twice per week during radiotherapy for general status, weight, blood counts, serum levels, and adverse events.

Scheduled analysis

The final analysis is scheduled at the end of the observation period.

Statistical analysis

Three- and 5-year DSFs of patients with postoperative advanced stage (stage III/IV) head and neck cancer, who were treated with radiotherapy alone after definitive surgery were 36% and 36%, respectively \(^2\text{a}\). Postoperative chemoradiotherapy with high-dose CDDP for patients with advanced stage revealed a 23% reduction in treatment failure risks associated with DFS compared with radiotherapy alone. The OS of patients with core high-risk
factors, e.g., microscopically involved surgical margin of the primary site and/or ENE, significantly improved through the concurrent use of high-dose CDDP during postoperative radiotherapy \(^2-^4\). The combined use of Cmab and DTX for patients with core high-risk factors during postoperative radiotherapy increased the 2-year DFS by 11% compared with patients who received high-dose CDDP \(^5\).

In this study, considering that CDDP intolerance refers to the poor condition of patients with core high-risk factors, the expected 2-year DFS is set at 35% for patients treated with postoperative radiotherapy alone, and Cmab and DTX could increase the survival rate by 20%. Thus, we set the expected 2-year DFS as 55%. Under the two-tailed significance level of 0.05 and power of 80%, the required sample size was calculated as 35 for this analysis.

**RESULTS**

**Trial status**

The UMIN Clinical Trials Registry (UMIN000031835) was completed on March 22, 2018. Patient enrollment started on April 1, 2018, and enrollment will close on March 31, 2021. The observation period will end on March 31, 2023. The expected schedule is shown in Fig. 2.
DISCUSSION

Head and neck cancers account for approximately 5% of all malignancies in Japan, and both the incidences and mortality rates are increasing, especially in patients aged above 50 years. The risk factors of head and neck cancer are smoking and alcohol consumption, and older patients have a longer history of these habits. Aging and a long history of smoking and/or alcohol consumption can induce cardiovascular disorders, pulmonary diseases, hepatic disorders, synchronous malignancies, and poor general condition. Additionally, Japanese patients with head and neck cancer show poorer renal functions with age, which limits the use of platinum-based drugs, especially CDDP. Such disadvantages restrict ideal treatment and are risk factors for complications during treatment.

Approximately 60% of patients with head and neck cancer present with advanced stage disease at their first visit, and surgery has been the definitive therapy for patients with advanced stage head and neck cancer, despite recent improvements in treatment and diagnostic instruments. Although surgery is a fundamental treatment for locoregional control, multidisciplinary approaches, including radiotherapy and chemotherapy, are improving prognoses.
Postoperative radiotherapy has been the standard adjuvant therapy for patients with high risks of locoregional recurrences and/or distant metastases \cite{12, 13}, but radiotherapy does not show dramatic prognostic improvements. After the report of Bernier et al. \cite{4}, the concurrent use of high-dose CDDP with postoperative radiotherapy has become the standard therapy for patients with core high-risk factors, e.g., those with microscopically involved surgical margins of the primary site and/or ENE. Although the accepted standard regimen is CDDP administration at the dose of 100 mg/m$^2$, once per every 3 weeks during radiotherapy, many patients with core high-risk head and neck cancer are not suited to receive this regimen owing to advanced age, poor renal function, hearing impairment, and/or poor general status.

In a randomized phase II trial, Harari et al. \cite{5} reported superior 2-year OS and DFS with less toxicity in patients with core high-risk factors who received postoperative radiotherapy with Cmab and DTX compared to those who received high-dose CDDP. The 2-year OS was 79% for the Cmab plus DTX arm and 69% for the CDDP arm, and the 2-year DFS was 66% and 57% for each arm, respectively. Grade 3/4 myelosuppression was observed in 14% of patients in the Cmab plus DTX arm and 28% of patients in the CDDP arm. Regarding
hematological adverse events, radiotherapy with Cmab alone indicated a small number of grade 3/4 events (3% of lymphopenia and 0.5% of anemia \(^{14,15}\)), and radiotherapy with DTX alone indicated an 8% rate of leukopenia, 4-4.8% of neutropenia, 56% of lymphopenia, and 4.8% of thrombocytopenia \(^{16,17}\) in patients with advanced head and neck cancer. Although the combined use of Cmab and DTX with radiotherapy tends to result in a high incidence of severe myelosuppression, it was a low percentage and was controllable compared to the myelosuppression events in patients who were administered CDDP.

Following this report, we applied this regimen as postoperative B-CRT in a small number of patients (11) with CDDP-intolerant core high-risk head and neck cancer and confirmed the efficacy and safety \(^1\). The 2-year DFS was 55%, which was the same as the expected 2-year DFS that was calculated from previous reports in this trial. No grade 4 adverse events were observed, and the grade 3 adverse events included oral mucositis (45%), aspiration (27%), radiation dermatitis (18%), leucopenia (9%), neutropenia (9%), lung infection (9%), and hyponatremia (9%). These adverse events were controllable and tolerable. Both Cmab and DTX are considered to have less usage restrictions compared with CDDP, and favorable interaction between the concurrent use of Cmab and DTX
in radiotherapy has been reported both in vivo and in vitro \(^\text{18}\). We consider that these merits make the combined use of Cmab and DTX as postoperative B-CRT suitable for patients with CDDP-intolerant core high-risk head and neck cancer. We will clarify the efficacy of this regimen in this phase II trial.

**Limitations**

This study has a single arm, with limited number of patients.

**COMPETING INTEREST**

We have no conflicts of interest.

**CONSENT FOR PUBLICATION**

Not applicable.

**ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

Ethics approval for this study was obtained from the Yokohama City University Institutional Review Board (#B180301010). Written informed consent was obtained from the participants in this study and for the publication of their data.

**AUTHOR’S CONTRIBUTIONS**
GN and NO collectively drafted the study protocol and ethical approval. GN participated in the central monitoring of data collection, trial management, and data analysis. HH, OS, MK, DS, NK, KY, YA, KS, YC, and TT participated in patient diagnosis, treatment, and follow-up. NO, who is the principal investigator of this study, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. MT is a statistician of this trial. All authors read the manuscript critically, made contributions, and approved the final manuscript.

AUTHOR’S INFORMATION

Department of Otorhinolaryngology, Head and Neck Surgery, Yokohama City University, School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan.

REFERENCES


FIGURE LEGENDS

Figure 1. Schema of patient enrollment, treatment, and evaluation.

Figure 2. Expected schedule is shown. Patient enrollment starts on April 1, 2018 for 3 years and will end on March 31, 2021. The observation period is set at 2 years, and the final analysis is set for March 31, 2023.