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Multicenter phase I/II study of chemoradiotherapy with high-dose CDDP for head and neck squamous cell carcinoma in Japan

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ABSTRACT

Objective: Recent data indicated that concurrent chemoradiotherapy (CCRT) using high dose cisplatin (CDDP) is the most useful treatment for advanced head and neck squamous cell carcinoma (SCC). Regarding the dose of CDDP, 100 mg/m^2 is most recommended in Western countries. However, in terms of a balance of efficacy and adverse events, appropriate dose of cytotoxic drugs such as CDDP may be different among the different ethnic groups. In this multicenter phase I/II study, we aimed to identify the optimal dose of CDDP in CCRT for patients with advanced head and neck SCC in the Japanese.

Methods: Patients were eligible for inclusion if they had head and neck SCC that was treated with radical CCRT comprising whole-neck irradiation of the primary lesion and level II–IV lymph nodes on both sides. For the phase I study, a CDDP dose was 70 mg/m^2 for level 0, 80 mg/m^2 for level 1, and 100 mg/m^2 for level 2. Maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) were examined by phase I trial, by which CDDP dose for phase II was determined. The primary endpoint for the phase II was CCRT completion rate, and the secondary endpoint was full-dose-CCRT completion rate, the percentage of patients receiving a total CDDP dose of ≥200 mg/m^2, response rate, and incidences of adverse events.

Results: A CDDP dose of 100 mg/m^2 was the MTD for phase I, and the recommended dose for phase II was 80 mg/m^2. Forty-seven patients were evaluated in the phase II trial. CCRT completion rate, full-dose-CCRT rate, and the percentage of patients receiving a total CDDP dose of ≥200 mg/

1. Introduction

In 1991, Department of Veterans Affairs Laryngeal Cancer Study Group reported that induction chemotherapy plus radiation

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m^2, were 93.6%, 78.7%, and 93.6%, respectively. One patient (2.1%) developed grade 2 renal dysfunction, and no patient developed febrile neutropenia or a grade 4 adverse event.

Conclusion: The present phase I study indicated that a CDDP dose of 80 mg/m^2 is the optimal dose in terms of safety. The phase II study revealed that CCRT completion rate, response rate, and rates of adverse events were not inferior for a CDDP dose of 80 mg/m^2 as compared with a dose of 100 mg/m^2, and a dose of 80 mg/m^2 is therefore recommended in CCRT for the Japanese.

This study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR; identification No. UMIN000010369).

(RT) for advanced laryngeal cancer could be effective in preserving the larynx in a high percentage of patients without compromising overall survival [1]. From this report, the treatment strategy for advanced head and neck squamous cell carcinoma (SCC) shifted from operation to concurrent chemoradiotherapy (CCRT). From 2000s, research results by Adelstein et al. and Forastiere et al. further accelerated this shift and the current evidence indicates that high-dose cisplatin (CDDP) + RT is the most useful treatment of choice for advanced head and neck SCC [2,3]. Regarding the dose of CDDP, 100 mg/m^2 is most recommended in Western countries and completion rate was ranged from 60 to 70% [3–6]. In terms of a balance of efficacy and adverse events, appropriate dose of cytotoxic drugs such as CDDP may be different among the different ethnic groups. Because of the different treatment tolerability in Asian patients, the amount of CDDP in the CDDP plus cetuximab regimen is being given at a lower dose than commonly used in Western countries, which does not result in reduced treatment outcome [7,8]. Completion rate of CCRT with CDDP at a dose of 100 mg/m^2 for Japanese patients was ranged from 40 to 60%, which was lower than those reported in Western countries [9–12]. There have been no studies that aimed to identify the most adequate amount of CDDP in CCRT for the Japanese patients. In this study, we conducted the Multicenter phase I/II study of chemoradiation with high-dose CDDP for head and neck squamous cell carcinoma in Japan to identify the optimal dose of CDDP for Japanese patients with head and neck SCC.

2. Patients and methods

2.1. Patients

Patients were eligible for inclusion if they had head and neck SCC that was treated with radical CCRT comprising whole-neck irradiation of the primary lesion and level II–IV lymph nodes on both sides. Additional criteria were age 20–75 years, an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, no previous chemotherapy, no complications or other cancer that might affect treatment of head and neck cancer, sufficient bone marrow function, no liver abnormalities, and creatinine clearance or estimated glomerular filtration rate (eGFR) $\geq$ 60 ml/min (Table 1). The study protocol was approved by the relevant institutional review boards. All patients provided written informed consent. This study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR; identification No. UMIN000010369).

2.2. Study design

We attempted to establish the optimal CDDP dose. Many centers use a CDDP dose of 80 mg/m^2 or 100 mg/m^2 [6,13,14]. We therefore compared doses of 80 mg/m^2 (level 1) and 100 mg/m^2 (level 2) in a type of phase I study (Table 2). To ensure safety, strict standards for dose reduction or chemotherapy termination and dose-limiting toxicity (DLT) were established (Table 3). After carefully evaluating adverse events, according to the Common Terminology Criteria for Adverse Events (CTCAE) Ver. 4.0, we examined maximum tolerated dose (MTD). The level below the MTD was defined as the recommended dose in phase II. If the MTD was not reached in level 2, 100 mg/m^2 would be selected as the recommended dose. The endpoint for the phase I trial was determination of the MTD and DLT. The primary endpoint for the phase II was CCRT completion rate, and the secondary endpoint was full-dose-CCRT completion rate, the percentage of patients receiving a total CDDP dose of $\geq$200 mg/m^2, response rate, and incidences of adverse events. We defined CCRT completion rate as the proportion of patients with planned RT completion and 3 chemotherapy courses while RT was delivered, even if CDDP dose was reduced. Full-dose-CCRT completion rate was defined similarly but did not permit dose reduction.

Table 1
Criteria for selection of patients.

Patients with head and neck squamous cell carcinoma (SCC)	
Patients with head and neck SCC treated with radical concurrent chemoradiotherapy comprising whole-neck irradiation of the primary lesion and level II–IV lymph nodes on both sides.	
Age 20–75 years	
Performance status 0–1	
First chemotherapy	
No complications or other active cancer that might affect treatment	
White blood cell count	$\geqq$3,000/mm^3
Neutrophils	$\geqq$1,500/mm^3
Platelets	$\geqq 10 \times 10^4$ /mm^3
Total bilirubin	Within normal range for the facility
AST, ALT	Within normal range for the facility
Creatinine	Within normal range for the facility
Creatinine clearance or eGFR	$\geqq$60 ml/min

AST: aspartate aminotransferase, ALT: alanine aminotransferase, eGFR: estimated glomerular filtration rate.

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