Chemoradiotherapy With Generic Cisplatin Formulations for Head and Neck Cancers

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ABSTRACT: The use of generic drugs has been increasing. However, studies of the safety of generic cisplatin (CDDP) for the treatment of head and neck cancer (HNC) have not been reported. This study investigated the treatment completion rates and incidence of CDDP-related adverse events in patients with advanced HNC treated with concurrent chemoradiotherapy (CRT) using generic CDDP. This study included 72 patients who received concurrent CRT using generic CDDP. The number of courses of CDDP was 3 in 45 patients, 2 in 19 patients, and 1 in 8 patients. During 154 courses of 80 mg/m^2 generic CDDP, grade 3/4 leukopenia in 21 (14%), neutropenia in 18 (12%), and hypochromia in 8 (5%) cases were reported. Grade 2 elevated serum creatinine occurred in 4 cases (3%), but no grade 3/4 elevated serum creatinine was reported. These results suggest that CRT using generic CDDP is well tolerated in patients with HNC.

KEYWORDS: Generic cisplatin formulations, chemoradiotherapy, head and neck cancer, chemotherapy

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Introduction

The use of generic drugs has recently been increasing with the aim of controlling medical costs. The use of generic cisplatin (CDDP), which plays a central role in the treatment of advanced head and neck cancer (HNC), is no exception.[1] Although generic drugs have the same active ingredients as innovator drugs, the excipients, stabilizers, and solvents are often different.

Drug patents include "process patents" granted for a manufacturing process and "formulation patents" granted for design of a drug formulation. Based on these patent periods, the excipients and dosage forms cannot be completely identical to those of the innovator drug. Efficacy tests must also demonstrate "no significant differences within a ±15% range from the innovator drug." Therefore, the incidence of adverse events may be different from the innovator drug, which can be a concern to physicians in clinical practice.

A greater incidence of renal toxicity has been reported for generic CDDP.[2] Moreover, because patients' background features differ depending on the cancer type, the same dose of CDDP does not necessarily result in the same adverse events. Moreover, safety studies of generic CDDP in patients with HNC treated in clinical practice have not been previously reported. The more widespread use of generic drugs in HNC treatment means that collection of adverse event data in patients with HNC treated in clinical practice is important.

Therefore, this study investigated treatment completion rates and the incidence of CDDP-related adverse events in patients with advanced HNC treated with concurrent chemoradiotherapy (CRT) using generic CDDP.

Patients and Methods

This study included 72 patients who received concurrent CRT using generic CDDP as part of their treatment for advanced HNC between September 2015 and February 2017 at the Department of Otolaryngology, Head and Neck Surgery at Tokyo Medical University Hospital. The generic CDDP formulation used was cisplatin for intravenous infusion (Maruko, Yakult Honsha Co., Ltd., Tokyo, Japan). The purpose of CRT included initial radical treatment of advanced HNC, postoperative irradiation, and treatment for recurrence. Postoperative irradiation was used in patients who had cervical lymph node metastases with extranodal spread or who had positive/close margins. The radiation dose for radical treatment was 2 Gy once daily, 33 to 35 times, for a total dose of 66 to 70 Gy. The postoperative irradiation dose in patients with free jejunal or gastric tube reconstruction was 1.8 Gy per fraction, 28 times, for a total dose of 50.4 Gy. In other cases, the radiation dose was 2 Gy per fraction, 30 times, for a total dose of 60 Gy.

In each case, CDDP was given a total of 3 times on days 1, 22, and 43 of radiotherapy. The standard dose of CDDP was 80 mg/m^2. In patients with a glomerular filtration rate (GFR) of 40 to <60 mL/min or grade 3 adverse events, 80% of this dose (64 mg/m^2) was given. For a GFR <40 mL/min or grade ≥4 adverse events, CDDP was discontinued. Patients who received CDDP were hydrated to maintain a daily urine output of ≥3000 mL. About 10 mEq of magnesium was also administered on days 1 to 3. No granulocyte colony-stimulating factor prophylaxis was given. Febrile neutropenia (FN) was defined as a neutrophil count <500/μL and a fever with an axillary temperature ≥37.5°C.

Table 1. Patient background characteristics.

Sex	
Male	58
Female	14
Age, y	
Mean	59
Range	24-78
Primary site	
Oral cavity	9 cases
Nasopharynx	5 cases
Mesopharynx	16 cases
Hypopharynx	19 cases
Larynx	7 cases
Salivary gland	11 cases
Nasal/paranasal sinuses	11 cases
External ear	2 cases
Stage (first medical examination)	
I	1 case
II	3 cases
III	15 cases
IV	53 cases
Purpose of CCRT	
Radical therapy	38 cases
CCRT after operation	30 cases
Recurrence	4 cases
Total no. of CDDP courses	
3 courses	45 cases
2 courses	19 cases
Single course	8 cases

Abbreviations: CCRT, concurrent chemoradiotherapy; CDDP, cisplatin.

Adverse events during each course of treatment were retrospectively evaluated. Adverse events were assessed based on the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0. Therapeutic effect of CRT was judged with endoscopy and image tests such as computed tomography and/or magnetic resonance imaging 6 to 8 weeks after the end of the therapy using Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1. The chemotherapy regimens were approved by the Chemotherapy Regimen Committee at Tokyo Medical University Hospital. Written informed consent was obtained from all patients for treatment and scientific use of the clinical data.

Results

Patient background characteristics

Table 1 summarizes the patient background characteristics. There were 58 men and 14 women, ranging in age from 24 to 78 years (mean age: 59 years). The primary tumor was cancer of the oral cavity in 9, nasopharynx in 5, mesopharynx in 16, hypopharynx in 19, larynx in 7, salivary glands in 3, nasal/paranasal sinuses in 11, and external ear in 2 patients. The stage at initial evaluation was stage I in 1, stage II in 3, stage III in 15, and stage IV in 53 patients. The purpose of CRT was initial radical treatment in 38, postoperative irradiation in 30, and treatment of recurrence after radical treatment in 4 patients.

Among the 38 patients who underwent initial radical treatment, 7 patients with cervical lymph node metastases with extranodal spread had neck dissection, followed by postoperative whole neck irradiation. In all, 27 cases (71%) were complete response (CR), 9 cases (24%) were partial response, 1 case (3%) was stable disease, and 1 case (3%) was progressive disease. Among the 30 patients who had postoperative irradiation, 5 had no flap reconstruction, 8 had free jejunal reconstruction, 1 had gastric tube reconstruction, 8 had free forearm flap reconstruction, and 8 had free rectus abdominis muscle reconstruction. The total radiation dose was 50 Gy in 1, 50.4 Gy in 9, 60 Gy in 23, 66 Gy in 1, and 70 Gy in 38 patients.

Total number of CDDP courses

Among the 72 patients, 45 had 3 courses, 19 had 2 courses, and 8 had 1 course of CDDP. Thus, the treatment completion rate for 3 courses was 63%. Among a total of 181 courses of CDDP, 154 were 80 mg/m^2 and 27 were 64 mg/m^2.

Adverse events

The adverse events are listed in Table 2.

80 mg/m^2 group. Leukopenia was grade 0 in 85 (55%), grade 1 in 3 (2%), grade 2 in 45 (29%), grade 3 in 20 (13%), and grade 4 in 1 (1%) case. Neutropenia was grade 0 in 115 (75%), grade 2 in 21 (14%), grade 3 in 17 (11%), and grade 4 in 1 (1%) case. One patient had FN. Hypochromia was grade 0 in 109 (71%), grade 2 in 37 (24%), and grade 3 in 8 (5%) cases. Elevated serum creatinine was grade 0 in 114 (74%), grade 1 in 36 (23%), and grade 2 in 4 (3%) cases.

64 mg/m^2 group. Leukopenia was grade 0 in 15 (56%), grade 2 in 10 (37%), and grade 3 in 2 (7%) cases. Neutropenia was grade 0 in 19 (70%) and grade 2 in 8 (30%) cases. None of the patients had FN. Hypochromia was grade 0 in 13 (48%), grade 2 in 12 (44%), and grade 3 in 2 (7%) cases. Elevated serum creatinine was grade 0 in 17 (63%), grade 1 in 7 (26%), and grade 2 in 3 (11%) cases.

Table 2. Adverse events.

	80 MG/M² (N = 154 COURSES)	64 MG/M² (N = 27 COURSES)
Leukopenia	Grade 0: 85 cases	Grade 0: 15 cases
	Grade 1: 3 cases	Grade 1: none
	Grade 2: 45 cases	Grade 2: 10 cases
	Grade 3: 17 cases	Grade 3: 2 cases
	Grade 4: 1 case	Grade 4: none
Neutropenia	Grade 0: 115 cases	Grade 0: 19 cases
	Grade 1: none	Grade 1: none
	Grade 2: 21 cases	Grade 2: 8 cases
	Grade 3: 17 cases	Grade 3: none
	Grade 4: 1 case	Grade 4: none
Hypochromia	Grade 0: 109 cases	Grade 0: 13 cases
	Grade 1: none	Grade 1: none
	Grade 2: 37 cases	Grade 2: 12 cases
	Grade 3: 8 cases	Grade 3: 2 cases
	Grade 4: none	Grade 4: none
Febrile neutropenia	1 case	None
Increased serum creatinine level	Grade 0: 14 cases	Grade 0: 17 cases
	Grade 1: 36 cases	Grade 1: 7 cases
	Grade 2: 4 cases	Grade 2: 3 cases
	Grade 3: none	Grade 3: none
	Grade 4: none	Grade 4: none

Discussion

Based on the highest level of evidence, CDDP is used as a standard treatment in CRT for radical treatment and postoperative adjuvant treatment in patients with locally advanced head and neck squamous cell carcinoma.[1,3,4] About 100 mg/m² of CDDP every 3 weeks is generally used worldwide, and use of this same dose has also been reported to be possible in Japanese patients.[5] However, from the standpoint of clinical tolerance, CDDP 80 mg/m² is often used even in cancer specialty hospitals in Japan.[6] Our hospital also uses 80 mg/m².

As a general guide, treatment outcomes are thought to improve at total CDDP doses ≥200 mg/m².[7,8] However, if adverse events were to increase with generic CDDP formulations, an increase in the number of patients receiving total doses <200 mg/m² might lead to worse treatment outcomes. With 3 courses of CDDP 80 mg/m², the total dose exceeds 200 mg/m². Among the 72 patients in this study, 45 patients (63%) tolerated 3 courses of CDDP, and CR rate of initial radical treatment patients was 71%. In cancer specialty hospitals in Japan, 50% of patients receiving this same regimen have been reported to tolerate 3 courses of CDDP, and CR rate was 74%.[6] The present results compared with those data suggest that CRT using generic CDDP can be well tolerated in clinical practice.

Use of generic versus innovator drugs can offer treatment at a lower cost to patients.[9] The year 2020 forecast for the global antitumor drug market, even if 88% of drugs are replaced by generic formulations, is estimated to be US $112 billion.[10] Therefore, the antitumor drug market is important for generic drugs. The cost for innovator CDDP in Japan (Randa Inj.; Nippon Kayaku Co., Ltd., Tokyo, Japan) is 10 939 yen (50 mg/100 mL), whereas the cost for the generic CDDP (Maruko) used in this study is less than half, only 4603 yen (50 mg/100 mL). From a medical cost standpoint, our hospital switched to generic CDDP in September 2015. There are no differences of the excipients between innovator CDDP and generic CDDP (Table 3). However, official date does not show these cisplatin purities clearly.

Nephrotoxicity is the dose-limiting toxicity of CDDP, and 7% to 40% of patients who receive CDDP have mild to moderate elevations in serum creatinine.[11,12] Sekine et al[2] compared

Table 3. Excipients of innovator and generic CDDP.

PRODUCT NAME	EXCIPIENTS	
	STABILIZERS—ISOTONIC AGENTS	PH-ADJUSTING AGENTS
Randa Inj. 10 mg/20 mL (innovator CDDP)	Sodium chloride (NaCl) 180 mg	Suitable hydrochloric acid
Maruko 10 mg/20 mL (generic CDDP)	Sodium chloride (NaCl) 180 mg	Suitable hydrochloric acid

Abbreviation: CDDP, cisplatin.

serum creatinine levels between patients receiving innovator CDDP and generic CDDP (80 mg). In men and women combined using the innovator drug, 88.6% had grade 0 to 1 and 11.5% had grade 2 to 3 events, whereas in those using the generic drug, 78.2% had grade 0 to 1 and 21.8% had grade 2 to 3 events. This represented a significant difference.[2] In the present patients using generic CDDP, 97% had grade 0 to 1 and 3% had grade 2 elevated serum creatinine, even better than that reported by Sekine et al with the innovator drug. The present results may be related to using 3 L/d of fluids for hydration together with magnesium as a renal protective agent.[13]

Oike et al[14] compared leukopenia between patients using innovator CDDP and generic CDDP. They reported leukopenia of grade 1 in 4.5%, grade 2 in 64%, and grade 3 in 32% of patients with innovator CDDP, and grade 1 in 4.5%, grade 2 in 27%, grade 3 in 59%, and grade 4 in 9% of patients with generic CDDP. The incidence of grade 3/4 events was significantly higher with generic CDDP.[14] In the present patients, grade 3/4 leukopenia and neutropenia occurred in 14% and 12% of patients, respectively. These are even better results than those reported by Oike et al with the innovator drug. The present findings should, to some extent, dispel concerns about increased adverse events with generic CDDP in patients with HNC treated in clinical practice.

This study does have some limitations. First, this was a single-center, single-arm study, and because all the CDDP in our hospital had already been switched to a generic formulation, a prospective single-center, randomized controlled study could not be conducted. In addition, the number of patients with HNC in a single center is limited. Moreover, besides the generic CDDP (Maruko) used in our hospital, 3 other generic CDDP formulations are currently marketed in Japan. Therefore, results from a multicenter study in which innovator and different generic CDDP formulations are compared may help to create an environment in which physicians in clinical practice can feel comfortable using these generic antitumor drugs in patients with HNC.

Conclusions

This study investigated the use of a generic CDDP formulation in CRT for HNC. The treatment completion rate for the scheduled 3 courses of CDDP was 63%. The present findings suggest that CRT using generic CDDP is well tolerated in patients with HNC treated in clinical practice.

Author Contributions

KT designed the study and is the corresponding author. RS wrote the manuscript. RS and ST collected and analyzed data. KT, ST, IO, HS, YK, RM and AS treated and followed up the patients. All authors read and approved the final manuscript.

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