

## Concurrent chemoradiotherapy with intravenous cisplatin and docetaxel for advanced oral cancer

Kotaro Sato<sup>1,2</sup>, Yasushi Hayashi<sup>1</sup>, Kazuyo Watanabe<sup>3</sup>, Ryoko Yoshimi<sup>1</sup>, and Hideharu Hibi<sup>2</sup>

<sup>1</sup>*Department of Oral and Maxillofacial Surgery, Nagoya Daini Red Cross Hospital, Nagoya, Japan*

<sup>2</sup>*Department of Oral and Maxillofacial Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan*

<sup>3</sup>*Department of Oral and Maxillofacial Surgery, Kariya Toyota General Hospital, Kariya, Japan*

### ABSTRACT

Concurrent chemoradiotherapy (CCRT) is a common treatment for advanced oral cancer, and its efficacy has been reported in many reviews. We have performed concurrent CCRT with intravenous cisplatin and docetaxel in patients with advanced oral cancer. The purpose of this report was to evaluate this treatment and to compare the outcome of this treatment with that of standard CCRT treatments for advanced head and neck cancer using intravenous administration.

The patients were treated for primary advanced oral squamous cell carcinoma in our department between February 2003 and November 2015. In all, 17 patients (14 men, 3 women) with stage III (2 patients) stage IVA (10 patients), and stage IVB (5 patients) oral cancer were treated. The patient ages ranged from 44 to 87 years (average age: 65.4 years). The follow-up duration ranged from 5 to 117 months (average follow-up duration: 41 months, median follow-up duration: 39 months). The primary cancer sites were the maxillary gingiva (7 cases), mandible gingiva (3 cases), buccal mucosa (3 cases), tongue (3 cases), and floor of the mouth (1 case). The 3-year and 5-year survival rates were 52.9% and 33.0%, respectively, and both the 3-year and 5-year locoregional control rates were 50.9% as determined by the Kaplan-Meier method. The response rate was 94% (CR: 8 cases: 47% and PR: 8 cases: 47%). The incidences of toxicity greater than grade 3 included dermatitis and stomatitis in 9 cases each (52.9%), anemia in 3 cases (18.7%) and liver dysfunction in 1 case (6.2%).

We found that the results of this therapy were equivalent to those of standard CCRT treatments for advanced head and neck cancer using intravenous administration, and the incidences of toxicity were lower than those of standard treatments. These findings suggested that this treatment is safe and useful for advanced oral cancer.

Keywords: cisplatin, docetaxel, concurrent chemoradiotherapy, oral cancer

#### Abbreviations:

CDDP: Cisplatin

DOC: Docetaxel

CCRT: Concurrent chemoradiotherapy

This is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Received: July 17, 2018; accepted: December 3, 2018

Corresponding Author: Kotaro Sato, DDS

Department of Oral and Maxillofacial Surgery, Nagoya University Graduate School of Medicine,  
65 Tsurumai-cho, Shouwa-ku, Nagoya, Aichi 466-8550, Japan

Tel: +81-52-744-2348, Fax: +81-52-744-2352, E-mail: kotarosato1123@med.nagoya-u.ac.jp

## INTRODUCTION

Chemoradiotherapy is widely performed for advanced oral cancer in the head and neck region to preserve organs and functions as well as to maintain aesthetics and quality of life. Combination therapies, including docetaxel, cisplatin and fluorouracil (TPF) therapy, are treatment strategies focusing on the lesion site and cell cycle. Although combination therapies are widely practiced, there are many cases in which treatments are interrupted due to adverse events. In our department, we have conducted intravenous chemoradiotherapy using cisplatin (CDDP) and docetaxel (DOC) for almost 20 years. Although intra-arterial chemoradiotherapy using CDDP and DOC has been widely performed, a few reports have examined the efficacy of intravenous CDDP and DOC administration.<sup>1,2</sup> In this report, we examined the survival rate, locoregional control rate, response rate and toxicity in patients who suffered from primary advanced oral squamous cell carcinoma and received concurrent chemoradiotherapy (CCRT) with intravenous CDDP and DOC. The purpose of this report was to evaluate this treatment and to compare the outcome of this treatment with that of standard CCRT treatments for advanced head and neck cancer using intravenous administration.

## METHODS

### *Patients*

Among the 170 primary oral cancer patients treated at the Department of Oral and Maxillofacial Surgery at Nagoya Daini Red Cross Hospital between February 2003 and November 2015, this retrospective analysis included 17 patients with T3 and T4 advanced oral squamous cell carcinoma who received CCRT with intravenous CDDP and DOC (Table 1). Patients who could follow-up as outpatients after treatment were included. This report was approved by the Nagoya Daini Red Cross Hospital institutional review board and the ethics committee (No. 9005).

### *Chemoradiotherapy*

Indications for this therapy included patients who did not wish to undergo surgical treatment for stages III and IV (T3 and T4) oral cancer as well as patients for whom surgery would be difficult due to the patient's medical history. Furthermore, in the full body examination, ① PS was 2 or less, ② bone marrow and liver function were normal, and ③ Ccr was 50 ml/min or greater (except for hemodialysis patients). The patients were intravenously administered CDDP (20 mg/m<sup>2</sup>/day) and DOC (15 mg/m<sup>2</sup>/day) at an interval of 1 week; the dose and schedule were determined by referring to a report by Tsao et al.,<sup>2</sup> and this regimen was performed for 6 courses to achieve the multiplication effect associated with CCRT considering patients' general conditions. The total doses of CDDP and DOC were 120 and 90 mg/m<sup>2</sup>, respectively. Radiation therapy consisted of 2 to 2.2 Gy/day/Fr × 30 times (Figure 1). One patient was a hemodialysis patient; although the dosage of DOC was not changed, CDDP was reduced by 50%, and we administered the drugs over 1 hour starting from 1 hour before dialysis. Dexamethasone, azasetron, domperidone, ramosetron and aprepitant were used to prevent nausea and vomiting. Filgrastim was injected subcutaneously on days 2 and 3 as a prophylaxis to prevent neutropenia.

### *Evaluation of antitumor effect and toxicity*

We evaluated the clinical antitumor effects of CCRT using the Response Evaluation Criteria in Solid Tumors guidelines. Toxicities that occurred during treatment were evaluated using the Common Terminology Criteria for Adverse Events version 4.0. Because the patient in case 9

**Table 1** Clinical characteristics of the patients

| Case | Age | Sex    | Location           | Histology | TNM classification                             | Stage | PS | Ccr(ml/min) |
|------|-----|--------|--------------------|-----------|--|-------|----|-------------|
| 1    | 64  | Male   | Tongue             | M         | T <sub>4a</sub> N <sub>2b</sub> M <sub>0</sub> | IV A  | 0  | 120.2       |
| 2    | 56  | Male   | Maxillary gingiva  | W         | T <sub>4a</sub> N <sub>0</sub> M <sub>0</sub>  | IV A  | 0  | 141.2       |
| 3    | 74  | Male   | Maxillary gingiva  | W         | T <sub>3</sub> N <sub>2c</sub> M <sub>0</sub>  | IV A  | 0  | 96.1        |
| 4    | 69  | Female | Maxillary gingiva  | W         | T <sub>3</sub> N <sub>0</sub> M <sub>0</sub>   | III   | 0  | 124.7       |
| 5    | 87  | Male   | Maxillary gingiva  | W         | T <sub>4a</sub> N <sub>0</sub> M <sub>0</sub>  | IV A  | 0  | 90.2        |
| 6    | 74  | Male   | Mandibular gingiva | M         | T <sub>4a</sub> N <sub>2c</sub> M <sub>0</sub> | IV A  | 0  | 83.9        |
| 7    | 58  | Male   | Floor of mouth     | W         | T <sub>3</sub> N <sub>2c</sub> M <sub>0</sub>  | IV A  | 0  | Dialysis    |
| 8    | 44  | Male   | Maxillary gingiva  | M         | T <sub>4a</sub> N <sub>2b</sub> M <sub>0</sub> | IV A  | 0  | 159.1       |
| 9    | 45  | Male   | Maxillary gingiva  | W         | T <sub>3</sub> N <sub>3</sub> M <sub>0</sub>   | IV B  | 0  | -           |
| 10   | 59  | Male   | Tongue             | M         | T <sub>4a</sub> N <sub>2c</sub> M <sub>0</sub> | IV A  | 0  | 70.8        |
| 11   | 65  | Male   | Maxillary gingiva  | M         | T <sub>4b</sub> N <sub>2b</sub> M <sub>0</sub> | IV B  | 0  | 87.3        |
| 12   | 64  | Male   | Buccal             | W         | T <sub>4b</sub> N <sub>2b</sub> M <sub>0</sub> | IV B  | 0  | 162.5       |
| 13   | 79  | Male   | Buccal             | M         | T <sub>4a</sub> N <sub>1</sub> M <sub>0</sub>  | IV A  | 0  | 99.7        |
| 14   | 52  | Male   | Mandibular gingiva | M         | T <sub>4b</sub> N <sub>2b</sub> M <sub>0</sub> | IV B  | 0  | 73.8        |
| 15   | 75  | Female | Buccal             | W         | T <sub>4b</sub> N <sub>2b</sub> M <sub>0</sub> | IV B  | 1  | 78.1        |
| 16   | 71  | Male   | Tongue             | W         | T <sub>3</sub> N <sub>0</sub> M <sub>0</sub>   | III   | 0  | 108.3       |
| 17   | 78  | Female | Mandibular gingiva | W         | T <sub>3</sub> N <sub>2c</sub> M <sub>0</sub>  | IV B  | 0  | 111         |

W : Well-differentiated, M : Moderately differentiated

|    | D+C   | D+C   | D+C   | D+C   | D+C   | D+C   |
|----|-------|-------|-------|-------|-------|-------|
| CT | ↓     | ↓     | ↓     | ↓     | ↓     | ↓     |
| RT | ↑↑↑↑↑ | ↑↑↑↑↑ | ↑↑↑↑↑ | ↑↑↑↑↑ | ↑↑↑↑↑ | ↑↑↑↑↑ |

CT : Chemotherapy (via vein)

- D : Docetaxel (DOC) 15mg/m<sup>2</sup>/day (Total: 90mg/m<sup>2</sup>)
- C : Cisplatin (CDDP) 20mg/m<sup>2</sup>/day (Total:120mg/m<sup>2</sup>)

RT : Radiotherapy

- 2~2.2Gy/day/Fr (Total:60~66Gy)

**Fig. 1** Treatment schedule

The patients were intravenously administered CDDP (20 mg/m<sup>2</sup>/day) and DOC (15 mg/m<sup>2</sup>/day) at an interval of 1 week; this regimen was performed for 6 courses (total dose: 120 mg/m<sup>2</sup> CDDP and 90 mg/m<sup>2</sup> DOC). For hemodialysis patients, although the dosage of DOC was not changed, CDDP was reduced by 50%, and we administered the drugs over 1 hour starting from 1 hour before dialysis. Radiation therapy consisted of 2 to 2.2 Gy/day/Fr × 30 times.

had no blood test data, toxicities measured by blood tests were examined among 16 patients and other toxicities were examined in 17 patients.

### Statistical analysis

Overall survival rate and locoregional control rate were evaluated using the Kaplan-Meier method with GraphPad Prism 5 software (GraphPad Software, La Jolla, CA). The overall survival

rate was calculated from the data from the first visit to the date of death or last follow-up visit. The patients who discontinued outpatient follow-up were treated as deaths.

## RESULTS

### *Therapeutic effects and outcomes (Table 2)*

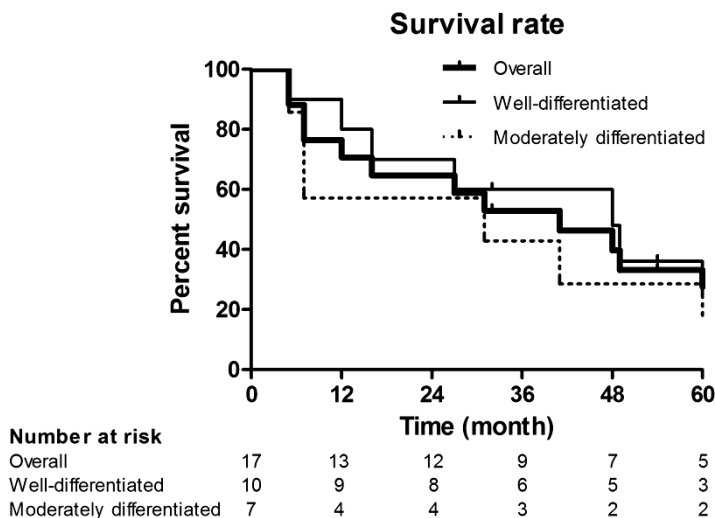
The patients included 14 males and 3 females, with ages ranging from 44 to 87 years (mean age: 65.4 years). The follow-up duration ranged from 5 to 117 months (average follow-up duration: 41 months, median follow-up duration: 39 months). The primary sites were the maxillary gingiva in 7 patients, mandibular gingiva in 3 patients, buccal mucosa in 3 patients, tongue in 3 patients and mouth floor in 1 patient. The histological findings were well differentiated in 10 patients and moderately differentiated in 7 patients. The T classifications were T3 in 6 patients, T4a in 8 patients and T4b in 3 patients, and the stage classifications were stage III in 2 patients, stage IVA in 10 patients and stage IVB in 5 patients. After CCRT, one patient underwent surgery, and 2 patients received chemotherapy because of recurrence at the primary site; one patient underwent surgery due to the occurrence of carcinoma in another site in the oral cavity. Four patients died as a result of the cancer, and 4 patients died due to other causes. In all, 5 patients discontinued treatment at our department during the follow-up period. According to the Kaplan-Meier method, the 3- and 5-year overall survival rates were 52.9% and 33.0%, respectively, and the 3- and 5-year survival rates for well-differentiated disease were 60% and

**Table 2** The details of treatment, effect and outcome

| Case | Total week | Total dosage<br>【CDDP/DOC (mg)】 | Radiation (Gy) |            | Effect of treatment | Follow-up period (Month) | Outcome |
|------|------------|---------------------------------|----------------|------------|---------------------|--------------------------|---------|
|      |            |                                 | Primary site   | Lymph node |                     |                          |         |
| 1    | 5          | 163/123                         | 66             | 66         | CR                  | 31                       | Do      |
| 2    | 7          | 275.5/206.5                     | 69             | -          | PR                  | 84                       | Ac      |
| 3    | 4          | 124/94                          | 66             | 66         | CR                  | 49                       | Do      |
| 4    | 5          | 150/120                         | 66             | -          | PR                  | 12                       | L       |
| 5    | 6          | 180/150                         | 66             | -          | CR                  | 63                       | L       |
| 6    | 5          | 150/100                         | 69.3           | 52.8       | CR                  | 41                       | Do      |
| 7    | 4          | 60/90                           | 41.4           | 41.4       | CR                  | 48                       | L       |
| 8    | 6          | 210/156                         | 66             | 66         | PR                  | 117                      | Ac      |
| 9    | 6          | 240/180                         | 66             | 66         | PD                  | 5                        | L       |
| 10   | 4          | 120/90                          | 60             | 60         | PR                  | 5                        | Dc      |
| 11   | 6          | 180/138                         | 60             | 60         | CR                  | 65                       | Do      |
| 12   | 6          | 187/156                         | 60             | 60         | CR                  | 54                       | Ao      |
| 13   | 6          | 194/145                         | 60             | 60         | CR                  | 7                        | Dc      |
| 14   | 6          | 199/129                         | 66             | 66         | PR                  | 7                        | Dc      |
| 15   | 6          | 128/96                          | 60             | 60         | PR                  | 27                       | Dc      |
| 16   | 6          | 204/156                         | 66             | 52.8       | PR                  | 32                       | Ac      |
| 17   | 6          | 192/141                         | 66             | 66         | PR                  | 16                       | L       |

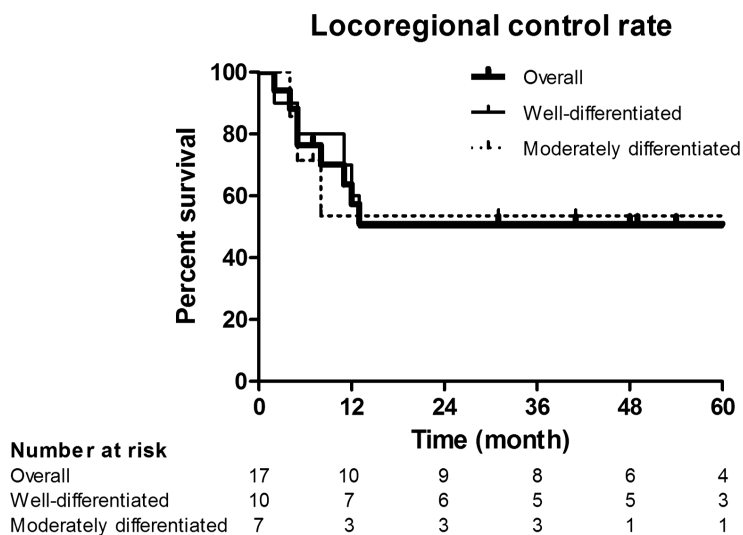
Ao: alive with outcomes; Ac: alive with cancer; Dc: death from cancer; Do: death from other causes  
L: lost to follow up

36%, while those for moderately differentiated disease were 42.8% and 28.5%, respectively. The 3- and 5-year overall locoregional control rates were both 50.9%; the 3- and 5-year locoregional control rates for well-differentiated disease were both 50%, while those for moderately differentiated disease were both 53.5%. The response rate was 94% (CR: 8 cases: 47%, PR: 8 cases: 47%) (Figures 2 and 3).



**Fig. 2** Survival rate

The 3- and 5-year overall survival rates were 52.9% and 33.0%, respectively. The 3- and 5-year survival rates for well-differentiated disease were 60% and 36%, while those for moderately differentiated disease were 42.8% and 28.5%, respectively.



**Fig. 3** Locoregional control rate

The 3- and 5-year overall locoregional control rates were both 50.9%, the 3- and 5-year locoregional control rates for well-differentiated disease were both 50%, and those for moderately differentiated disease were both 53.5%.

*Toxicities (Table 3)*

Grade 3 or 4 dermatitis and mucositis occurred in 9 patients each (52.9%), anemia occurred in 3 patients (18.7%) and liver dysfunction occurred in one patient (6.2%). We applied a topical steroid ointment to treat dermatitis and prescribed an azunol/xylocaine gargle and NSAIDs to reduce the pain associated with mucositis. In cases of difficult pain control, we prescribed narcotic analgesics. Because of the difficulty in oral intake due to mucositis, 5 patients (29.4%) underwent insertion of a nasal-gastric tube, and 4 patients (23.5%) received central venous nutrition. Although grade 3 anemia occurred in cases 1 and 10, it was improved by follow-up alone; therefore, no treatment was administered. Grade 4 anemia occurred in case 17 and was improved by administration of red blood cell concentrate; the patient was able to continue CCRT thereafter. Liver dysfunction occurred in case 15 and was improved by administration of glycyrrhizic acid.

**Table 3** Toxicity

| Toxicity         | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Total number of patients |
|------------------|---------|---------|---------|---------|--------------------------|
| Fever            | 6       | 4       | 0       | 0       | n=17                     |
| Mucositis        | 1       | 7       | 9       | 0       | n=17                     |
| Dermatitis       | 4       | 4       | 9       | 0       | n=17                     |
| Leukopenia       | 7       | 5       | 0       | 0       | n=16                     |
| Neutropenia      | 1       | 2       | 0       | 0       | n=16                     |
| Thrombocytopenia | 2       | 0       | 0       | 0       | n=16                     |
| Anemia           | 5       | 7       | 2       | 1       | n=16                     |
| Creatinine       | 4       | 0       | 0       | 0       | n=16                     |
| AST/ALT          | 3       | 1       | 1       | 0       | n=16                     |
| Vomiting         | 1       | 0       | 0       | 0       | n=17                     |
| Diarrhea         | 0       | 0       | 0       | 0       | n=17                     |

## DISCUSSION

The development of surgical techniques, such as the free flap graft, has allowed for the surgical treatment of patients with advanced head and neck cancer. However, in cases with a wide resection area, the patient's cosmetic and functional burden is also increased. Additionally, some patients cannot tolerate surgery due to their medical histories and ages, and others do not desire to undergo surgery. Due to the development of anticancer drugs, CCRT is now one of the main treatments for advanced head and neck cancer. We performed CCRT through the intravenous administration of a combination of CDDP and DOC and examined several parameters. Because CDDP enhances the sensitivity of radioresistant hypoxic cells<sup>3</sup> and inhibits the healing of sublethal injuries and the potential lethal damage resulting from radiation,<sup>4</sup> its radiation sensitivity enhancing effect has been noted. Additionally, DOC showed an increased cell killing effect in a study using squamous cell carcinoma cell lines,<sup>5</sup> and the combined use of DOC with radiation and CDDP is effective. The usefulness of CDDP and DOC in intra-arterial CCRT for cancers in the head and neck region has been reported.<sup>6</sup> However, as with intra-arterial chemoradiotherapy, adverse events such as complications accompanying catheter placement and cerebrovascular disorders have also been reported.<sup>7,8</sup> Because the identification of feeding arteries in extensively developed tumors may be difficult, drug delivery may also be difficult. Moreover, extravasation and phlebitis are associated with intravenous drug administration, and strict management

is required when administering anticancer agents, such as in the case of intravenous therapy; however, the operation is relatively simple and the treatment results in a decreased patient burden.

According to the National Comprehensive Cancer Network, intravenous CCRT is recommended for category 1 advanced head and neck cancer; the 3-year survival rate is between 37 and 42.6%, the 5-year survival rate is between 22 and 55.1%, the 3-year local control rate is 37.6%, and the 5-year local control rate is between 47.6 and 67.7%.<sup>9-11</sup> The toxicity rates according to the Common Terminology Criteria for Adverse Events<sup>11</sup> were 45.3% for grade 3 or higher mucositis, 42.1% for leukopenia, 17.9% for anemia, 15.8% for nausea/vomiting and 3.2% for platelet count reduction. Although comparisons may be difficult due to the small number of cases in this report, the 3- and 5-year overall survival rates were 52.9% and 33.0%, respectively, and the 3- and 5-year overall locoregional control rates were both 50.9%. We obtained results similar to those of the standard treatment for advanced head and neck cancer using intravenous administration. Although the survival rate was lower for moderately differentiated than well-differentiated disease, the locoregional control rate was almost the same. Thus, this therapy might be useful for lower grade cancers. Many patients achieved locoregional control, including the patient in case 1, in whom primary hepatocellular carcinoma was observed during follow-up. Although the patient died at 31 months after CCRT, recurrence was not observed at the primary site. Additionally, relapse was not found in the oral cavity for patients who died from other diseases (cases 3, 6, and 11) and in patients who discontinued outpatient visits (cases 5 and 7). In the terminal stage of advanced oral cancer, an increase in the tumor size resulting in a decrease in aesthetics and quality of life is typically observed. Although it is unknown whether our treatment method achieved a marked prolongation of life in patients with distant metastasis, it is thought that by providing locoregional control, this therapy sufficiently contributed to maintaining the aesthetics and quality of life at the terminal stage.

The frequency of toxicity, especially hematologic toxicity, was low. In cases 1 and 10, grade 3 anemia was thought to be caused by dermatitis and chronic inflammation due to mucositis. After CCRT, no additional treatment was performed, and the dermatitis and mucositis healed. For case 17, in which grade 4 anemia occurred, GIF resulted in a diagnosis of a gastric ulcer, which was thought to be due to bleeding from the same section. As hemostasis was obtained, the condition improved after administration of omeprazole and red blood cell concentrate. In case 15, grade 3 liver dysfunction was considered to be due to the effect of DOC and was improved by glycyrrhizic acid administration. The decrease in leukopenia was lower than that in other reports, possibly due to the G-CSF preparation, and prophylactic administration of an antiemetic agent may have contributed to a reduction in the number of patients who experienced vomiting. Among the patients who experienced difficulty eating due to mucositis pain, 5 patients (29.4%) underwent nasal-gastric tube placement and 4 patients (23.5%) received central vein nutrition. One study reported the necessity of a nasal-gastric tube with taxane-based chemoradiotherapy,<sup>2</sup> and it is thought that early measures for patients who have difficulty eating are necessary. In this report, the nasal-gastric tube and central venous catheter were withdrawn in all cases before discharge, and all patients were discharged after regaining the ability to eat rice porridge and a chopped meal. During CCRT for case 7 (a hemodialysis patient), DOC was administered at the usual dose and CDDP was reduced to half of the normal dose, which is consistent with the guidelines<sup>12</sup> of Japanese Society of Nephrology. Regarding intravenous administration of CDDP in dialysis patients, Miyagawa et al.<sup>13</sup> reported that serious toxicities were not observed when CDDP was administered at a dose of 25 mg/m<sup>2</sup>, and Ayabe et al.<sup>14</sup> reported similar results for a dose of 50 mg/kg body weight. According to Hirata et al.,<sup>15</sup> to maintain the CDDP concentration in the blood, administration after dialysis or 1 hour before dialysis is recommended rather than administration during dialysis. We administered CDDP according to this recommendation, and

the treatment was completed without serious toxicity.

Based on the above findings, the present therapy showed good results for both the survival rate and locoregional control rate, and because of the low toxicity, it may be an appropriate therapeutic method for maintaining organ function, aesthetics and quality of life in patients with advanced oral cancer. Because a small number of cases were included in this report, the analysis of this treatment was limited; thus, further reports with additional cases are necessary to accurately evaluate this treatment.

## CONFLICTS OF INTEREST STATEMENT

None declared.

## REFERENCES

1. Kitamoto Y, Akimoto T, Ishikawa H, et al. Acute toxicity and preliminary clinical outcomes of concurrent radiation therapy and weekly docetaxel and daily cisplatin for head and neck cancer. *Jpn J Clin Oncol*. 2005;35(11):639–644.
2. Tsao AS, Garden AS, Kies MS, et al. Phase I/II study of docetaxel, cisplatin, and concomitant boost radiation for locally advanced squamous cell cancer of the head and neck. *J Clin Oncol*. 2006;24(25):4163–4169.
3. Richmond RC, Simic MG. Effect of radiation on cis-dichlorodiammineplatinum (II) and DNA in aqueous solution. *Br J Cancer Suppl*. 1978;3:20–23.
4. Dritschilo A, Piro AJ, Kelman AD. The effect of cis-platinum on the repair of radiation damage in plateau phase Chinese hamster (V-79) cells. *Int J Radiat Oncol Biol Phys*. 1979;5(8):1345–1349.
5. Pradier O, Rave-Frank M, Lehmann J, et al. Effects of docetaxel in combination with radiation on human head and neck cancer cells (ZMK-1) and cervical squamous cell carcinoma cells (CaSki ). *Int J Cancer*. 2001;91(6):840–845.
6. Robbins KT, Kumar P, Harris J, et al. Supradose intra-arterial cisplatin and concurrent radiation therapy for the treatment of stage IV head and neck squamous cell carcinoma is feasible and efficacious in a multi-institutional setting: results of Radiation Therapy Oncology Group Trial 9615. *J Clin Oncol*. 2005;23(7):1447–1454.
7. Yokoyama J. Present role and future prospect of superselective intra-arterial infusion chemotherapy for head and neck cancer. *Gan To Kagaku Ryoho*. 2002;29:169–175. (in Japanese)
8. Watanabe M, Kano M, Matsui T, Nomoto Y, Ohtani I. Side effects of superselective cisplatin intra-arterial infusion chemotherapy for head and neck cancer. *Jibi To Rinsyo*. 2003;49:15–20. (in Japanese)
9. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol*. 2003;21(1):92–98.
10. Bourhis J, Sire C, Graff P, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. *Lancet Oncol*. 2012;13(2):145–153.
11. Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol*. 2013;31(7):845–852.
12. Japanese Society of Nephrology. <https://cdn.jsn.or.jp/guideline/pdf/2016-cancer-guideline-170706.pdf>. Accessed June 08, 2018.
13. Miyakawa M, Sugimoto K, Ohe Y, Masuoka H, Miyahara T. Pharmacokinetics of cis-dichlorodiammine platinum (II) in patients undergoing hemodialysis. *Gan To Kagaku Ryoho*. 1987;14:2491–2495. (in Japanese)
14. Ayabe H, Uchikawa T, Kimino K, Tagawa Y, Kawahara K, Tomita M. Pharmacokinetics of cisplatin and vindesine in a patient with chronic renal failure undergoing hemodialysis. *Gan To Kagaku Ryoho*. 1989;16:3283–3285. (in Japanese)
15. Hirata J, Kato S, Kin M, Tanaka K. Kouganzai. *Yakuji*. 1999;41:87–100. (in Japanese)