Docetaxel and Nedaplatin Chemotherapy for Advanced Oral Squamous Cell Carcinoma: A Case Report

Yasunori Ariyoshi,1 Masashi Shimahara,1 Yoshitaka Kurisu,2 and Motomu Tsuji2

1Department of Oral Surgery, Osaka Medical College, Takatsuki, Osaka 569-8686, Japan
2Department of Surgical Pathology, Osaka Medical College Hospital, Takatsuki, Osaka 569-8686, Japan

Correspondence to:
Yasunori Ariyoshi
E-mail: ora009@poh.osaka-med.ac.jp

Abstract
A new chemotherapy regimen consisting of intravenous docetaxel (60 mg/m²) and nedaplatin (70 mg/m²) was performed in a 51-year-old patient with unresectable squamous cell carcinoma of the tongue (T4N0M0). After 2 courses of chemotherapy and follow-up irradiation, complete tumor regression was observed (clinical CR). Except for short-term grade 4 neutropenia and mucositis, severe toxicities were not observed. Excision of scar tissue at the tumor site was performed without causing tongue dysfunction, and pathological CR was confirmed. In the present case, DOC/CDGP chemotherapy followed by radiotherapy was effective against locally advanced squamous cell carcinoma of the tongue.

Keywords: combination chemotherapy, docetaxel, nedaplatin, oral squamous cell carcinoma

Introduction
Recently, trials of preoperative taxane-based chemotherapy combined with carboplatin have achieved high-response rates in patients with advanced head and neck cancer (1, 2). In addition, reports have indicated that carboplatin-associated thrombocytopenia was less severe than was expected in patients treated with a combination of carboplatin and paclitaxel (3). Nedaplatin (cis-diammine-glycocolate platinum, CDGP) is a new platinum analogue that was developed in Japan while docetaxel (DOC) is an inhibitor of microtubule depolymerization that has been used to treat head and neck cancer patients, and studies have reported its effectiveness (4, 5).

In the present patient, locally advanced squamous cell carcinoma (SCC) of the tongue showed a good response to chemotherapy with the combination of DOC and CDGP.

Report of a case
A 51-year-old Japanese man was referred to our clinic because of a painful mass on the left side of the tongue. About a year prior to this referral, he had had left anterior tongue pain, and he had consulted a dentist. He received trimming of sharp edges of certain teeth and was given a mouth piece to wear. However, the pain was not relieved, and a mass developed and increased in size, so ten months later, he visited another oral surgery clinic, which referred him to our department. His past medical history was non-contributory.

On examination, there was no swelling of the left side of the face and no associated lymphadenopathy. Intraoral examination revealed a 2.0×3.0 cm indurated, ill-defined mass with mucosal ulceration at its center; the mass occupied the left anterior one third of the ventral surface of the tongue (Fig. 1-a). On palpation, the indurated tender mass extended beyond the midline. The patients had limited tongue movements and difficulty in speaking. Panoramic radiogram showed no bone destruction. MRI revealed a tumor mass in the left anterior portion of the tongue (Fig. 2). Ga and Tc-99m scintigraphy revealed no abnormal uptake, except on the left side of the tongue. Incisional biopsy was performed, and a histopathological diagnosis of well differentiated SCC was made (Fig. 1-b). The clinicopathological diagnosis was tongue SCC (T4N0M0, stage IVa), so
Fig. 1. a: Intraoral view at the first visit. There is an endophytic indurated mass that occupies the left anterior one third of the ventral surface of the tongue. b: Histopathological findings on incisional biopsy. Histopathological examination reveals well differentiated squamous cell carcinoma. (hematoxylin and eosin stain, original magnification ×49)

Fig. 2. a: Fast spin echo T1-weighted image (T1WI). b: Fast spin echo T2-weighted image (T2WI). On MRI, a relatively well circumscribed mass was demonstrated, showing a low signal intensity on T1WI and a high signal intensity on T2WI.

subtotal glossectomy was required for radical surgery. Accordingly, we performed neoadjuvant chemotherapy for down-staging of the tumor.

Two courses of combination chemotherapy with DOC and CDGP were performed (Fig. 3). Written informed consent was obtained before chemotherapy started. Treatment consisted of DOC (60 mg/m²) as a one-hour intravenous infusion followed by (CDGP 70 mg/m²) as a one-hour infusion. Intravenous dexamethasone (8.0 mg) was given for one hour before DOC infusion to prevent a hypersensitivity reaction. Infusion of CDGP was followed by i.v. hydration with 1,000 mL of physiological saline. Approximately one week after the first course of chemotherapy, a decrease in tumor size was noted. In addition, the limitation of tongue movement, speech dysfunction, and tongue pain were all improved. Nine days after treatment, Grade 2 (NCI common toxicity criteria) leucopenia (Grade 4 neutropenia) was observed. Mucositis was not a severe problem after the first course, but severe alopecia occurred although it recovered 10 weeks after the completion of 2 courses of chemotherapy. There was no nausea, which treatment with an oral 5-HT3 antagonist probably prevented, and no hypersensitivity reaction. Three weeks after the first course of chemotherapy, tumor re-growth was noted. Therefore, a second course of chemotherapy was given four weeks after the first
course was completed. The tumor showed a decrease in size as it did after the first course. On the eighth day after the second course of chemotherapy, Grade 4 leucopenia (Grade 4 neutropenia) was observed, but it could be controlled with granulocyte colony stimulating factor (G-CSF). In both courses, no other severe side effects occurred except oral mucositis. The tumor continued to decrease in size, and the chemotherapy achieved a clinical complete response (Fig. 4). To avoid the need for prophylactic neck dissection, radiotherapy (a total dose of 45 Gy) was performed to the upper neck and the tongue. After these preoperative treatments, there was no detectable tumor mass, but an indurated, scar-like lesion (0.5 cm in diameter) was palpable on the left side of the tongue (Fig. 5-a). Under general anesthesia, this indurated area was excised. Histopathological examination of the resected specimen showed no residual tumor cells (Fig. 5-b). His postoperative course was uneventful, and there was no limitation of tongue movements and no difficulty in speaking.

Discussion

In patients with previously untreated, locally advanced carcinoma, chemotherapy has been combined with radiotherapy and/or surgery in an attempt to increase loco-regional control, decrease distant metastasis, and improve survival (6). Clinical trials of neoadjuvant chemotherapy for advanced SCC, mainly employing cisplatin (CDDP)/5-fluorouracil (5-FU) with or without docetaxel (5), have been reviewed, and effectiveness for organ preservation has been reported (7).

Recently, studies of phase II trials of DOC and CDDP chemotherapy in patients with head and neck SCC (8-11) reported that this combination chemotherapy was effective for locally advanced, recurrent, and metastatic cancer while toxicity ranged from tolerable to substantial. CDGP is more effective than CDDP against SCC (12) while nephrotoxicity is

Fig. 4. Laboratory data and tumor size during treatment course. Severe neutropenia was observed approximately 1 week after chemotherapy, but there was no anemia or thrombocytopenia. The tumor decreased in size after each course.

Fig. 5. a: Intraoral view on completion of chemoradiotherapy. b: Microscopic appearance of the resected specimen. Only a scar-like indurated area measuring 0.5 cm in diameter remained at the tumor site. Histopathological examination of the resected specimen revealed pathological complete response (hematoxylin and eosin stain, original magnification ×49).
less common with CDGP than CDDP. DOC has demonstrated in vivo and in vitro activity against a variety of solid mammalian tumors (13), as a well a lack of cross-resistance with CDDP in several tumor cell lines (14). Based on these findings, we used a DOC/CDGP combination as neoadjuvant chemotherapy for locally advanced, non–resectable oral carcinoma. In the present case, 2 courses of DOC/CDGP therapy were effective for down-staging the tumor, and we could preserve the tongue both morphologically and functionally after radical surgery. A characteristic of this therapy is that it achieves a rapid response, but the duration of response is also short. Many groups have repeated DOC/CDGP chemotherapy every three weeks (8–11). In the present case, myelosuppression recovered range within three weeks, and tumor re-growth was noted at this time. These findings suggest that if side effects have subsided within three weeks, the next course should be administered.

Both DCGP and DOC have myelosuppression as a dose–limiting toxicity. We found that G–CSF could control neutropenia. In their phase II study of DOC/ CDDP chemotherapy, Specht et al. (9) found that moderate–to–severe neutropenia was the most common problem, but it was generally of short duration. In addition, this chemotherapy regimen rarely induced thrombocytopenia. Glisson et al. (11) also reported on a phase II trial of DOC/CDDP chemotherapy; Grade 4 neutropenia was observed in 71% of their patients, but thrombocytopenia was only observed in 3%. It has been reported that the combination of paclitaxel/carboplatin causes less thrombocytopenia than expected (3). In the present case, Grade 4 neutropenia, which was of short duration and well controlled by G–CSF, was observed after each course of chemotherapy, but there was no neutropenic fever. In addition, there was no thrombocytopenia during either course of treatment. Thus, the hematologic toxicity of this chemotherapy regimen targeted neutrophils, and the dose–limiting toxicity was neutropenia in our patient. Other side effects, including nephrotoxicity, hypersensitivity, diarrhea, and nausea, were not problematic, but the patient suffered from severe mucositis and severe alopecia that recovered approximately 10 weeks after the completion of chemotherapy.

The aim of neoadjuvant chemotherapy is to reduce the tumor burden prior to definitive local control. There are potential advantages and disadvantages of such chemotherapy (15). The main disadvantages are the delay of definitive surgery and the risk of creating drug–resistant tumor–cell clones. Therefore, it is important to determine which drugs the tumor shows sensitivity to in individual patients before starting chemotherapy. In addition, the toxicity of the chemotherapy drugs should be tolerable and of short duration. In the present patient, the most severe toxicity of chemotherapy was neutropenia, but it was tolerable and short–term. Also, the response to therapy was rapid. The characteristic advantage of CDGP therapy compared with CDDP therapy is that hydration is unnecessary. In conclusion, DOC/CDGP chemotherapy may become a useful neoadjuvant regimen for locally advanced oral carcinoma, but further trials are required to standardize this newly established drug combination.

**Conclusion**

This article reports on a case of advanced squamous cell carcinoma of the tongue that was treated with a combination chemotherapy of docetaxel and nedaplatin. The patient showed good response without uncontrollable side effects. This newly established chemotherapy is useful for advanced, non–resectable oral squamous cell carcinoma.

**References**


3. Kearns CM, Egorin MJ: Considerations regarding the