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ORIGINAL ARTICLE

Multicenter phase 2 study of induction chemotherapy with docetaxel and nedaplatin for oral squamous cell carcinoma

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Abstract
Purpose To determine the clinical and hisotological efficacy and toxicities of induction chemotherapy with docetaxel (DOC) and nedaplatin (CDGP) for oral squamous cell carcinoma (OSCC) in the preoperative setting.
Methods A total of 30 patients with locally advanced but operable OSCC were enrolled. Combination induction chemotherapy consisted of DOC 60 mg/m^2 followed by CDGP 100 mg/m^2.
Results All patients received one cycle of chemotherapy. In the clinical assessment, ten patients achieved partial response for an overall response rate of 33.3% (95% CI, 16.4–50.2%). Histological assessment of surgical specimens showed an overall response rate of 56.6% (95% CI, 38.9–74.3%). Although severe neutropenia was observed in 90% of patients, only one patient (3.3%) experienced severe infection. Toxicities associated with this regimen did not interfere with planned radical surgery.
Conclusions A single cycle of preoperative combination chemotherapy with DOC and CDGP showed moderate histological activity with an acceptable safety profile for the planned radical surgery. Further studies testing more cycles before surgery might be more appropriate.

Keywords Neoadjuvant chemotherapy · Squamous cell carcinoma · Docetaxel · Nedaplatin · Oral cancer

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Introduction

Oral squamous cell carcinoma (SCC), particularly early stage disease, is potentially curable with the standard treatment of surgery and/or radiation, but most patients present with locally advanced disease and their prognosis is poor. To improve their outcome, chemotherapy has been integrated into a combination therapeutic approach involving surgery and radiotherapy. Induction chemotherapy is often used prior to other modalities and might facilitate subsequent surgery or radiation [1, 2]. Previous randomized studies have failed to demonstrate a survival advantage with the addition of induction chemotherapy to locoregional therapy consisting of surgery and/or radiation therapy in patients with locally advanced head and neck SCC [2, 3], although some studies have suggested a possible benefit of induction chemotherapy in patients with oral SCC [4–6]. Recently, however, interest in induction chemotherapy has been renewed, as the introduction of a taxane into induction chemotherapy regimens showed that the addition of active

induction chemotherapy may further improve outcome by enhancing locoregional and distant control [2, 7–10]. Induction chemotherapy should be the subject of further clinical research. Active chemotherapy regimens may have been suboptimal. Sometimes, we experienced the discrepancy between the clinical and histological responses. Therefore, the development of an intensive and rational regimen with a clinical as well as histological high-tumor remission rate in the preoperative setting is required.

Previously, we have shown in the phase I study that induction chemotherapy with 60 mg/m^2 DOC and 100 mg/m^2 CDGP for up to two doses had an encouraging response rate with manageable toxicity [11]. Toxicities associated with this regimen did not interfere with planned radical surgery. Therefore, in this study, we conducted a multicenter, prospective, non-randomized phase II study to determine the clinical and histological efficacy and toxicities of preoperative chemotherapy with DOC and CDGP in patients with oral SCC.

Patients and methods

Study design

We conducted a non-comparative phase II study to evaluate the efficacy and toxicity of preoperative induction chemotherapy with DOC and CDGP. The response rate of either single-agent DOC or CDGP for head and neck carcinoma has been reported to be 20.6 or 42.2%, respectively. Therefore, the null hypothesis of a true response rate of 40% or lower was tested against the alternative hypothesis of a true response rate of 65% or higher. The sample size was calculated as 25 patients, with a one-sided alpha-level of 0.05 and 80% power, using the Southwest Oncology Group Statistical One Arm Binomial Tool [12]. With an expected non-assessable rate of 10%, 28 or more patients were to be enrolled.

Eligibility criteria

Patients with a resectable oral SCC (histologically proven and previously untreated) of late T2 (diameter more than 3 cm), T3, or T4 [13] were registered for DOC and CDGP combination preoperative chemotherapy. Eligibility criteria for chemotherapy were: (1) age between 20 and 75 years (patients aged >76 years were allowed if major organ functions were preserved), (2) Eastern Cooperative Oncology Group performance status (PS) score of 2 or less, (3) adequate bone marrow function (white blood cell count from 4,000 to 12,000/μl, neutrophil count of 2,000/μl or more, platelet count of 100,000/μl or more, and hemoglobin level of ≥10.0 g/dl), (4) adequate hepatic function (total serum bilirubin level ≤1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase less than or equal to twice the upper limit of the normal range), (5) adequate renal function (serum creatinine ≤1.5 mg/dl and creatinine clearance rate ≥60 ml/min). Patients were excluded if they had active infections, active second malignancy, severe heart diseases, interstitial pneumonia or lung fibrosis, severe pleural effusion or pericardial effusion that required drainage, fever ≥38°C, symptomatic brain metastasis, severe psychological disease, and possible pregnancy.

Written informed consent was obtained from each patient. The Institutional Review Board and/or ethics committee of each participant center reviewed and approved the protocol prior to commencement.

Treatment protocol

The treatment regimen and dosage were based on the results of phase I analysis of the drug combination. Patients received a 1-h intravenous infusion of DOC on day 1. After completion of the DOC infusion, CDGP was administered intravenously for another hour followed by ≥1,000 ml hydration. All patients received intravenous 5-HT$_3$ antagonist before the administration of anticancer drugs and 8 mg dexamethasone on days 0, 1 and 2. Additional antiemetic treatment was given as necessary, using an additional 5-HT$_3$ antagonist and/or prochlorperazine. Granulocyte colony-stimulating factor (G-CSF) was administered once a day if the neutrophil count was below 500/μl or febrile neutropenia (fever ≥38°C and neutrophil count of <1,000/μl) was observed. G-CSF was stopped if the neutrophil count was >5,000/μl. All patients received one cycle of chemotherapy, and a second cycle was allowed on day 29 if an improved treatment outcome was expected and the patient again satisfied the eligibility criteria.

Evaluation of response and toxicity

Pretreatment evaluation included a baseline history and physical examination, complete blood cell count with differential and routine chemistry profiles, urine analysis, assessment of renal function, chest radiograph, and electrocardiogram. Physical examination and complete blood cell count measurements with differential and routine chemistry profiles were performed at least once a week during chemotherapy. The primary site was evaluated using computed tomography or magnetic resonance imaging at least before and in the fourth week during chemotherapy.

Clinical tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [14]. Histological response was assessed using surgical specimens obtained from planned radical surgery carried out after the completion of

chemotherapy. Histological responses were graded using the criteria proposed by Shimosato et al. [15]: grade 0, no visible effect; grade I, no structural destruction of the tumor despite some visible cytotoxic effects; grade IIa, extensive distribution of morphologically well-preserved cancer cells amounting to ≥25% of the cross-sectional area; grade IIb, a relatively small area of morphologically well-preserved cancer cells amounting to <25% of the cross-sectional area; grade III, only cancer cells appearing non-viable being visible, or grade IV, no visible cancer cells.

Adverse events were categorized and graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC version 3.0).

Results

Patient characteristics

Thirty eligible patients were enrolled in this study between March 2005 and June 2007. The patient characteristics are summarized in Table 1. Two patients aged over 75 years (76 years) with good PS and major organ functions were among those enrolled. The study population was comprised of 7 women and 23 men, with a median age of 63.5 years (range 20–76 years). All patients received one cycle of chemotherapy and no patient received a second cycle. The planned radical surgery for their tumors was carried out in the forth week after completion of chemotherapy.

Response

The outcome of chemotherapy is shown in Table 2. In the clinical assessment, ten patients achieved PR for an overall response rate of 33.3% [95% confidential interval (CI), 16.4–50.2%]. Eighteen patients had no significant change in tumor size and two patients had progressive disease. Histological assessment of surgical specimens showed that eight patients were classified as grade 1, five grade 2a, ten grade 2b, four grade 3, and three grade 4 according to the criteria [15] proposed by Shimosato et al. The overall response (grade 2b or higher) rate in histological assessment was 56.6% (95% CI, 38.9–74.3%).

Toxicity

The toxicities are summarized in Table 3. Severe (grade 3 or 4) neutropenia was frequent, occurring in 90%, and febrile neutropenia (grade 3) occurring in 10% of patients. Twenty-four patients received G-CSF support. Neutropenia reached a nadir on day 8 (median) and resolved within 5 days. Other hematological toxicity was rare, and two cases of anemia (grade 2 and 3) and no thrombocytopenia were observed. Two patients experienced infection (grade 3 and grade 2). They successfully recovered with medical interventions and underwent the planned operation uneventfully. Most of the non-hematologic toxicities were mild to moderate in severity. Alopecia was the most

Table 1 Patient characteristics

Total number of patients enrolled	30
Age	
Median (years)	63.5
Range (years)	20–76
Gender	
Male	23
Female	7
Performance status (ECOG)	
0	29
1	1
Primary site	
Tongue	16
Upper gum	8
Oral floor	3
Lower gum	2
Cheek mucosa	1
T-classification	
T2 (late)	12
T3	4
T4	14
Clinical stage	
II	6
III	4
IVa	20

Table 2 Clinical and histological response

Response	No. of patients (%)	Response rate* (95% confidential interval)
Clinical		
CR	0 (0.0)	33.3% (16.4–50.2%)
PR	10 (33.3)	
SD	18 (60.0)	
PD	2 (6.7)	
Histological		
Grade 4	1 (3.3)	56.6% (38.9–74.3%)
Grade 3	4 (13.3)	
Grade 2b	10 (33.3)	
Grade 2a	5 (16.7)	
Grade 1	8 (26.7)	

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *CI* confidential interval

* Clinical response rate = (CR + PR)/30; histological response rate = (grade 4 + 3 + 2b)/30

Table 3 Incidence of toxicity according to NCI common toxicity criteria

Toxicity	Grade				Prevalence of grade 3/4 (%)
	1	2	3	4	
Blood					
Neutropenia	0	3	4	23	90
Febrile neutropenia	0	0	3	0	10
Thrombocytopenia	0	0	0	0	–
Anemia	0	1	1	0	3.3
Infection					
Infection with grade					
3 or 4 neutropenia	0	0	1	0	3.3
Infection other	0	1	0	0	–
Gastrointestinal					
Nausea/vomiting	8	0	3	0	10
Anorexia	5	8	2	0	6.7
Diarrhea	8	0	1	0	3.3
Others					
Alopecia	8	13	0	0	–
Fatigue	11	2	3	0	10
Hyponatremia	2	0	4	0	13.3
Transaminase	0	1	0	0	–
Fever	1	0	0	0	–
Arthritis	1	0	0	0	–
Edema limb	1	0	0	0	–

frequent non-hematologic toxicity (70%) followed by fatigue (53.3%) and anorexia (50%). Severe (grade 3 or 4) hyponatremia occurred in four patients (13.3%), nausea/vomiting in three (10%), fatigue in three (10%), anorexia in two (6.7%), and diarrhea in one (3.3%). All non-hematologic toxicities were reversible and had no impact on the planned surgical treatment.

Discussion

Docetaxal (DOC) is a new anticancer agent classified as a taxane. It has demonstrated significant activity against head and neck cancer with objective response rates in the range of 27–42% [16–19], being among the most active drugs for head and neck cancer. Recently, randomized trials have reported that the addition of a docetaxel to the most commonly used regimen (cisplatin and fluorouracil, PF chemotherapy) has further improved the response rate and survival outcome without increasing toxicity, compared with PF alone [8, 9]. These results suggested that integrating docetaxel in the induction setting might lead to increasing anti-tumor effects with tolerated adverse effects.

Nedaplatin [*cis*-dammine-glycolate platinum (CDGP)] is a second-generation platinum derivative developed in Japan and has demonstrated potent anti-tumor activity against lung, esophageal, testicular, gynecological, and head and neck cancers. Some in vitro studies have shown that CDGP had equivalent anti-tumor activity to cisplatin in lung [20], ovarian [21], and head and neck cancers [22] with lower nephro- and neuro-toxicity than cisplatin. A phase II study examining CDGP as a treatment of head and neck cancers showed a good response rate of 43.9% with mild and infrequent nephrotoxicity [23]. Platinum primarily acts as an alkylating agent, while DOC stabilizes microtubules and inhibits mitosis; therefore, a combination of DOC and platinum should be expected to result in additive anti-tumor effects and non-overlapping toxicities profiles. Yamada et al. [24] evaluated the sequence dependency of anti-tumor efficacy and toxicity in combination therapy of taxane (paclitaxel) and platinum (cisplatin, carboplatin, and CDGP) against Lewis lung carcinoma. They reported that the combination effect of taxane and CDGP was significantly higher than that of taxane and cisplatin or taxane and carboplatin. These results suggested that combination chemotherapy with taxanes and CDGP may be associated with promising results and may be required.

In the results of this study, a single cycle of preoperative combination chemotherapy with DOC and CDGP for advanced but operable oral SCC achieved a clinical response rate of 33.3% (95% CI, 16.4–50.2%) and a histological response rate of 56.6% (95% CI, 38.9–74.3%). In an early phase II study of combination chemotherapy of DOC (60 mg/m^2) and CDGP (90 mg/m^2) in patients with resectable oral SCC, single cycle chemotherapy showed an overall clinical response rate of 33.3% and an overall histological response rate of 66.9% [25]. Our result was compatible with these results. Previously, some studies have explored the combination of DOC and other platinum (cisplatin) in locally advanced, recurrent or metastatic SCC of the head and neck, reporting response rates from 33 to 53.7% [26–29]. These rates are similar to or slightly higher than the response rate in our study; however, in this study, all patients received only a single cycle of chemotherapy, while patients in previous trials received a median of 2–5 cycles of chemotherapy. The best number of treatment cycles is uncertain, but complete response rates increased with each successive cycle up to cycle 4 in the study by Paccagnella et al. [30]. In the results of this study, the overall response rate of 56.6% was obtained in the histological assessment, a rate that was higher than that of clinical assessment. The discrepancy between the clinical and histological responses is unknown and might be due to a delay in histological absorption and the reconstruction of destroyed cancer tissues. It is possible that successive cycles of histologically active combination chemotherapy of DOC and

CDGP might lead to a promising higher clinical response rate. As often happens in daily clinical practice, most of patients with respectable tumor undergo medical and tumor assessment preoperatively and must be on the waiting list for primary surgery. In this study, we aimed to develop the regimen of induction chemotherapy that could be completed during this "necessary" interval, which could possibly be administered in the outpatient setting. Consequently, in the results of this study, all patients received only single cycle of induction chemotherapy during this "necessary" time, and the clinical response was not as good as we expected. Further studies testing more cycles before surgery might be more appropriate.

The toxicity produced by combination chemotherapy with 60 mg/m^2 DOC followed by 100 mg/m^2 CDGP was significant but manageable. Toxicities associated with this regimen did not interfere with the planned radical surgery. As expected from the results of our phase I study [11], neutropenia was the most frequent and severe toxicity. All patients experienced grade 2 or more neutropenia, which was generally short-lived and was resolved by G-CSF support within 5 days. Although severe neutropenia (grade 3 or 4) was observed in 90% of patients, only one patient (3.3%) experienced severe infection associated with grade 3 or 4 neutropenia. This patient was successfully treated with medical intervention. There was no other severe hematological toxicity except for two cases of reversible anemia.

Alopecia was the most frequent non-hematologic toxicity with an incidence of 70%, followed by fatigue and anorexia with an incidence of 56.7 and 50.0%, respectively. These side effects were manageable and reversible. Nausea and vomiting were expected to be the most frequent and severe non-hematologic toxicities, but appeared to be prevented by the prophylactic use of 5-HT$_3$ antagonist and corticosteroids. Hypersensitivity reactions, skin changes, and signs of fluid retention are infrequent but known toxicities attributed to DOC [17, 27], but these were not observed in our study. Prophylactic use of corticosteroids may play a role in preventing these toxicities. Other toxicities were rare and manageable; however, severe (grade 3) hyponatremia requiring intravenous sodium infusion was observed in three patients. This problem has not been reported by others and requires attention.

For head and neck SCC, the standard induction regimen was the combination of cisplatin and continuous infusion of 5-fluorouracil (5-FU), and the regimen has shown overall response rates of 60–80% [30–34]. Recent randomized trials added docetaxel to PF chemotherapy (TPF regimen) and reported significant superior response and survival than the PF regimen [8, 9]. The three-drug regimen (TPF) will be considered the standard of care for induction chemotherapy in head and neck SCC. However, in this study, we tested the two-drug regimen with DOC and CDGP, excluding 5-FU in the induction chemotherapy in the preoperative setting. The reasons are as follows: First, it was suggested that continuous infusion of high dose 5-FU might be associated with the possible mucosal toxicity and prolonged morbidity, which would be problematic factors when definitive local treatment was scheduled [2, 29]. Second, single-day infusion of docetaxel and nedaplatin is advantageous because the need for ambulatory pumps and/or prolonged hospitalization for infusional 5-FU is avoided. Third, some studies compared the efficacy of using taxane in the place of 5-FU, as is typically used in PF therapy [35, 36]. No significant difference in the response rate or overall survival was seen between taxane/platin (paclitaxel/cisplatin or docetaxel/nedaplatin) therapy and PF therapy. These data encouraged us to test the efficacy and safety of the two-drug regimen with DOC and CDGP, which could be administered in the outpatient setting. However, as shown in this study, the response rate of a single cycle of DOC and CDGP was lower than that of PF as well as TPF therapy. As stated above, the lower response rate in this study was probably associated with the significantly limited cycle of chemotherapy. Randomized phase III trials comparing the multi cycle of induction chemotherapy of taxane/platin versus taxane/platin plus 5-FU are necessary.

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