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Efficacy of Paclitaxel and Cetuximab in Recurrent/Metastatic Oral Cancer Cases Following Superselective Intraarterial Chemoradiotherapy: A Retrospective Cohort Study

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Abstract. *Background/Aim: The therapeutic efficacy of the paclitaxel (PTX) + cetuximab (Cmab) combination regimen was investigated in patients with recurrence or metastasis after superselective intraarterial chemoradiotherapy (SSIACRT) for oral cancer, and the safety was retrospectively examined. Patients and Methods: All enrolled patients with advanced oral cancer or who had refused surgery over 10 years from December 2012 to December 2022 underwent SSIACRT for 6 to 9 weeks [cisplatin (CDDP): total 160-630 mg/m^2 and radiotherapy: total 50-70 Gy]. Nine cases (tongue cancer, maxillary gingival cancer, and mandibular gingival cancer; three cases each) were subjected to PTX + Cmab therapy. Recurrence or metastases were observed within six months after the onset of treatment, complicating the conduct of salvage surgery. Cmab (first dose: 400 mg/m^2 and second and following doses: 250 mg/m^2) and PTX (80 mg/m^2) were administered weekly. Results: The overall response rate was 44.4% (four of nine cases), and the disease control rate was 88.9% (eight of nine cases), whereas the median progression-free survival was seven months, and the overall survival was 11 months. Grade 3-4 adverse events were neutropenia in 33.3% of the cases, leukopenia in 55.6%, anemia in 22.2%, and acneiform skin rash in 22.2%. Based on the above, PTX + Cmab therapy for recurrent and metastatic cases after SSIACRT had comparable results to other second-line modalities and enabled to cope with the side effects of myelosuppression. Conclusion: PTX + Cmab therapy may be an effective treatment mode for recurrent or metastatic head and neck cancer resistant to CDDP after SSIACRT treatment.*

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Key Words: Superselective intraarterial chemoradiotherapy (SSIACRT), recurrent/metastatic oral cancer, cetuximab, paclitaxel, cisplatin unresponsiveness/intolerance.

Simultaneous chemotherapy and radiotherapy incorporating superselective intraarterial chemoradiotherapy (SSIACRT) have shown an excellent local control rate, making organ preservation possible in advanced oral cancer (1, 2). However, because it is applied in advanced cancer cases, residual tumors or distant metastases due to treatment resistance are frequently observed (2). In recurrence or metastasis cases after SSIACRT, high cisplatin (CDDP) doses are already administered, although there is a high possibility of resistance to platinum drugs as well. Because radiotherapy is also used together with the combination regimen, it is difficult to implement in local recurrence cases. There are few reports on the effects of this type of therapy in recurrence and metastasis after SSIACRT, and it is often difficult to elucidate them. In this study, the effects of paclitaxel (PTX) + Cetuximab (Cmab) therapy on oral cancer recurrence and metastasis were explored after intraarterial infusion of concurrent chemoradiotherapy (CCRT) with high-dose CDDP. The reason for the high efficacy of PTX + Cmab is that cetuximab enhances the effect of PTX by down-regulating p65 expression induced by paclitaxel (3). PTX + Cmab may be used in patients for whom platinum is not recommended or when platinum resistance develops. Furthermore, because it shows a high response rate, PTX + Cmab may be administered not only as

first-line treatment for recurrent and metastatic head and neck squamous cell carcinoma (R/M HNSCC) (4, 5) but also as second- and third-line treatment. In fact, it is one of the most effective regimens after Immune checkpoint inhibitors (ICI) therapy according to many reports (6-8) and is considered the primary treatment option for R/M HNSCC. In cases of recurrence or metastasis within six months after platinum therapy, the disease is considered to resistant to platinum agents, so we chose PTX + Cmab this time based on the report by Hitt *et al*. (9). The therapeutic effects reflected in the treatment outcomes were retrospectively evaluated, including adverse events.

Patients and Methods

Enrolled patients were subjected to SSIACRT with CDDP from December 2012 to December 2022 for inoperable cases, those who refused surgery, and those involving cervical lymph node metastases, where intervention was performed with neck dissection. All enrolled patients received SSIACRT for six to nine weeks [cisplatin (CDDP): total 160-630 mg/m2 and radiotherapy: total 50-70 Gy]. PTX + Cmab combination therapy was applied in nine cases of inoperable oral squamous cell carcinoma (SCC) with recurrence or metastases occurring within six months after the completion of treatment. There were five male and four female patients, and the average age was 66.4 years. The primary sites of malignant lesions were the tongue in three cases, maxillary gingiva in three cases, and mandibular gingiva in three cases, and the stage before SSIACRT according to T classification of primary tumors was T3 in two cases, T4a in four cases, and T4b in three cases. A recurrence site coincided with a primary tumor in eight cases and that of a lung metastasis in one case (Table I). The dosage and schedule were elaborated based on Hitt *et al*.'s phase II study (9), with an initial intravenous Cmab dose of 400 mg/m^2, followed by 250 mg/m^2 weekly conjugated with 80 mg/m^2 PTX. If a pre-administration blood test showed a white blood cell count <2,000/mm^2 or a neutrophil count <1,000/mm^2, PTX was discontinued, and only Cmab therapy was performed. If the conditions were met in a blood sample taken before a subsequent administration, the PTX dose was reduced to 60 mg/m^2. Due to the hepatic metabolism of PTX, a dose decrease was also considered if liver damage accompanied by high bilirubin or elevated levels of hepatic enzymes was detected (10). The indicated therapy was prolonged until signs of progressive disease (PD) or intolerable toxicity were found (Figure 1). The evaluation parameters were Cmab administration period, adverse events, progression-free survival (PFS), and overall survival (OS), and they were retrospectively investigated based on medical records. Treatment efficacy was estimated according to the new guidelines for determining the treatment of solid tumors [Response Evaluation Criteria in Solid Tumors (RECIST) guidelines revised version 1.1] (11). Adverse events were assessed using Common Terminology Criteria for Adverse Events version 4.0 (12). OS and PFS rates were determined using the Kaplan–Meier method. The end of PFS was outlined as disease advancement or death caused by any factor, and the end of OS referred to the latter. The ethics committee of Nippon Dental University School of Life Dentistry at Niigata (Approval number ECNG-R-542; Niigata, Japan) approved the present study.

Table I. *Patient characteristics (n=9). All patients had undergone radiotherapy concurrent with cisplatin.*

	No. (%)
Sex	
Male	5 (56)
Female	4 (44)
Age, years	
Mean	64 (48–82)
Histology (SCC)	
Differentiation	
Well-differentiated	5 (56)
Moderately differentiated	3 (33)
Poorly differentiated	1 (11)
Stage	
III	2 (22)
IV	7 (78)
Primary site	
Tongue	3 (33)
Gingiva	6 (67)
Recurrence/metastatic site	
Primary lesion	8 (89)
Lung metastasis	1 (11)

Informed consent was obtained from all patients included in the study. The exact time when the patients' medical records were accessed is April 2024.

Results

The median (range) duration of PTX + Cmab therapy was 17 (3-47) cycles, and that of maintenance with PTX combination and Cmab alone was 18 (5-47) cycles. The antitumor effect was found in four (44.4%) cases as partial response (PR), four (44.4%) as stable disease (SD), and one (11.1%) as PD, whereas the response rate was 44.9%. The disease control rate was 88.9% (Table II). The median PFS was seven months, and the OS was 11 months (Figure 2). Grade 3 or higher events were neutropenia (33.3%), leukopenia (55.6%), anemia (22.2%), and acneiform rash (22.2%; Table III). In one infusion reaction case, a decrease in blood pressure was detected during the first injection, but this was improved by reducing the administration rate by 50%, and subsequent administrations were performed as usual. In one patient, Cmab alone was administered from the fifth treatment due to bone marrow suppression. No hypomagnesemia or interstitial pneumonia was diagnosed in any case.

Discussion

SSIACRT is one of the treatment modalities for advanced oral cancer, and its effectiveness has been demonstrated in previous studies (1, 2). Mitsudo *et al*. performed definitive arterial infusion CCRT in 112 individuals with stage III and

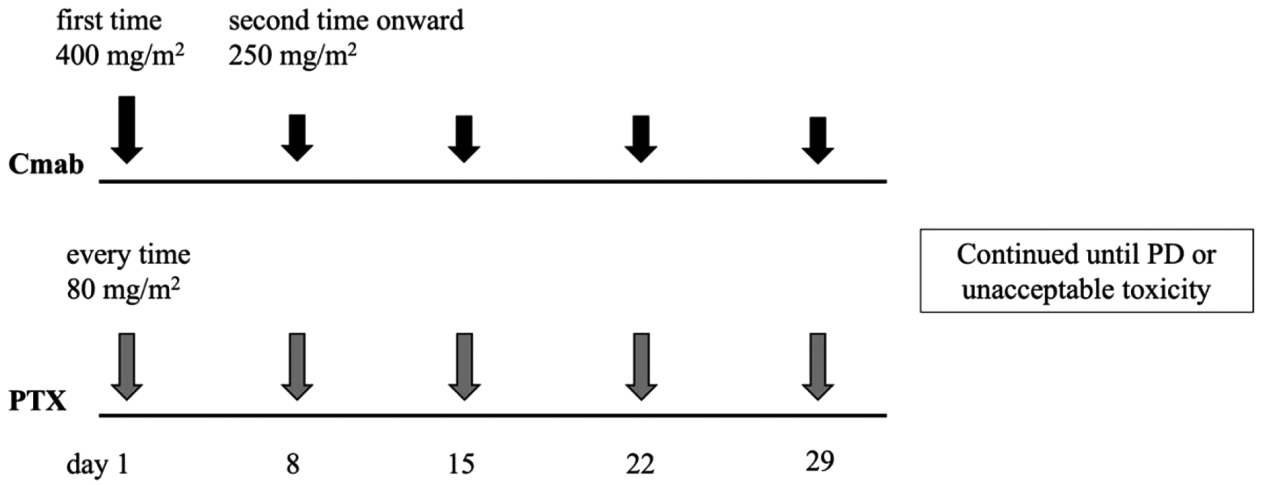

Figure 1. *Administration of cetuximab (Cmab) and paclitaxel (PTX) combination regimen in our department.*

Table II. *Antitumor effect.*

Nine cases			
Best therapeutic effect	CR	0 cases	0%
	PR	4 cases	44.4%
	SD	4 cases	44.4%
	PD	1 case	11.1%
ORR			44.4%
DCR			88.9%

ORR: Overall response rate; DCR: disease control rate; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Table III. *Adverse events (CTCAE version 4.0).*

Adverse event	All grades		≥Grade 3	
	No. cases	%	No. cases	%
Leukopenia	7	77.8	5	55.6
Neutropenia	7	77.8	3	33.3
Anemia	9	100	2	22.2
Loss of appetite	9	100	0	0
Nausea	6	66.7	0	0
Peripheral neuropathy	0	0	0	0
Hypomagnesemia	0	0	0	0
Acneiform eruption	9	100	2	22.2
Skin hyperpigmentation	9	100	0	0
Interstitial pneumonia	0	0	0	0
Infusion reaction (hypotension)	1	11.1	0	0

IV oral cancer, and the outcomes were favorable, with a 5-year cumulative survival rate of 71.3% (stage III: 83.1% and stage IV: 64.5%) (2), whereas a previous report also showed good results with SSIACRT (7, 13). However, most cases in which SSIACRT was performed were advanced forms resistant to treatment, and a considerable number of cases of recurrence and distant metastases were reported (1, 2). To date, there is limited data regarding the prognosis of patients who have undergone SSIACRT for treatment and have not been completely cured. In recurrence or metastases in oral cancer that cannot be treated with surgery or radiotherapy, there is a low possibility of a complete cure, and the prognosis is approximately two to four months if untreated (14). Furthermore, Vermorken *et al*. reported that the survival rate in conditions treated with platinum-containing drug therapy as a primary regimen is six to nine months (15). The median survival time drops to 3.5 months in patients who received drug therapy, including platinum drugs, but did not respond to it (15). These studies suggested that after IACRT treatment, the options for its scheme are restricted due to the use of radiotherapy and high-concentration CDDP, and the prognosis is less promising. In this study, the median PFS and OS rates were seven and 11 months, respectively. In other studies of Cmab + PTX combination regimen, PFS was 3.9 to 7.7 months, and OS was 7.6 to 16.8 months (Table IV), comparable to previous studies (5, 9, 16-21). This proposes a potentially high efficacy of PTX and Cmab for platinum-resistant SCC of the head and neck (SSCHN) after SSIACRT. Furthermore, when the cases of PTX + Cmab combination therapy were compared with other reports of Cmab + CDDP + 5-FU combination therapy, no significant differences were found in the latter, with the median progression-free survival being 4.2 to 6.6 months and the median overall survival being 7.3 to 12.6 months (15, 20, 22-24).

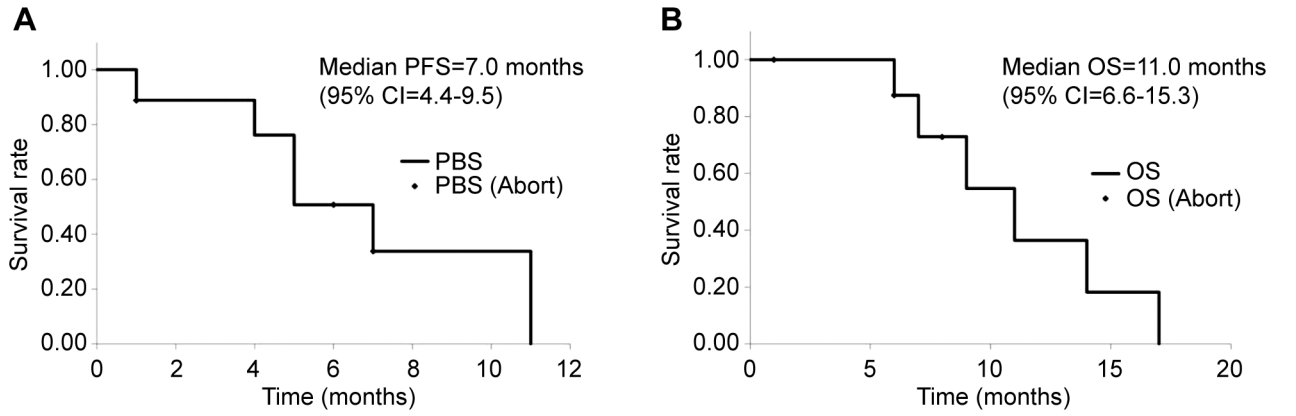

Figure 2. *Kaplan–Meier curve of progression-free survival (PFS) (A) and overall survival (OS) (B) of patients on cetuximab (Cmab) and paclitaxel (PTX) chemotherapy after recurrence/metastases after superselective intraarterial chemoradiotherapy.*

Table IV. *Comparison of overall survival (OS) and progression-free survival (PFS) rates.*

	No. cases	CR (%)	PR (%)	SD (%)	PD (%)	Antitumor effect (%)	PFS (months)	OS (months)
Hitt *et al*. (2012) (9)	46	22	33	26	11	54	4.2	8.1
Peron *et al*. (2012) (16)	42	5	33	36	17	38	3.9	7.6
Jimenez *et al*. (2013) (17)	20	5	50	–	–	55	5.4	9.1
Sosa *et al*. (2014) (18)	33	0	55	24	21	55	4.0	10.0
Pellini Ferreira *et al*. (2016) (19)	59	2	45.8	30	15	47.5	7.7	13.2
Nakano *et al*. (2017) (20)	49	–	–	–	–	45	6.0	16.8
Fushimi *et al*. (2020) (5)	59	14	32	27	27	46	5.7	11.8
Motai *et al*. (2021) (21)	22	9	27	36	27	36	4.0	9.0
This case	9	0	44.4	44.4	11.1	44.4	7.0	11.0

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; PFS: progression-free survival; OS: overall survival.

The drug with a competitive efficacy that was included in the treatment regimen in this study is nivolumab, an anti-PD-1 antibody. CheckMate 141 is a phase III study performed in 361 individuals with recurrent/metastatic SCCHN, in whom disease progression was evident within six months after administration of platinum-based medications, disregarding tumor PD-L1 expression status (25). The trial compared the efficacy of nivolumab to conventional chemotherapeutic agents: methotrexate, docetaxel, or Cmab. Nivolumab monotherapy resulted in longer OS than in that with the latter, with a median OS of 7.5 *versus* 5.1 months, respectively. Furthermore, the overall response rate (ORR) was 13.3% with nivolumab *versus* 5.8% with standard treatment. In the Asian nivolumab subcohort of CheckMate 141, nine of 23 (39%) patients exhibited some extent of tumor regression, with an ORR of 26.1% according to RECIST. In contrast, four of nine patients who received PTX and Cmab in this study had tumor regression, with an ORR of 44.4% according to RECIST. In addition, Pareeek *et al*. administered nivolumab to patients with recurrent metastasis who had progressed after one or more chemotherapy regimens including platinum agents and reported that the PFS was three months and the OS was eight months from the date of first administration. These results suggest that PTX+Cmab is a non-inferior treatment to nivolumab for recurrent metastasis after SSIACRT (26). In addition, it suggested that PTX + Cmab combination therapy may exert an antitumor effect comparable or superior to nivolumab, particularly in tumor size decrease, being more effective in patients with rapid tumor growth. Wakasaki *et al*., reported that the ORR and disease control rate (DCR) of patients who received PTX+Cmab after nivolumab as salvage chemotherapy were 53.3% and 91.1%, respectively, and the estimated median OS and PFS from the first administration of PTX+Cmab were 13.5 months and 8.1 months, respectively. Based on these results, it is necessary to consider administering PTX+Cmab after nivolumab when the tumor growth rate is slow (27). However, these are data based on a noncomparative analysis of smaller cohorts.

In this study, the most common grade 3/4 toxicities were rash (22%), anemia (22%), and neutropenia (33%). The frequency of the former was higher than in previous studies (18, 20). This may be explained by a greater rate of formerly prescribed regimens with Cmab than in the previous with a greater total period of Cmab administration. Anemia was also more often observed in previous studies (18, 20). This may be due to the inclusion of only patients subjected to large CDDP doses with SSIACRT. However, there was high tolerability of complications.

Important aspects of palliative chemotherapy cover improving or maintaining quality of life (QOL). Although QOL was not analyzed in the sample, one (11%) patient was shifted from PTX and Cmab to Cmab maintenance therapy due to hypotension, presumably caused by PTX therapy. To attain maximum benefits with good QOL, it is important to select drugs considering the patient's conditions, such as the need for rapid tumor regression or its absence. In this study, the combination therapy of Cmab + PTX was effective, enabling disease management without serious adverse events. However, because the number of evaluated cases is small, it is necessary to consider a higher number of cases in a further investigation.

Conflicts of Interest

Kaname Sakuma, Tomoyuki Kii, Toko Machida, Yosuke Kikuchi, Masaki Yoda, Shuji Toya, and Akira Tanaka declare that they have no conflict of interest in relation to this study.

Authors' Contributions

KS, TK, YK, MY, and TM contributed substantially to the conception and design, acquisition of data, and analysis and interpretation of data. ST and AT were involved in drafting and revising the manuscript for important intellectual content.

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