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Lack of Survival Advantage in Patients with Advanced, Resectable Squamous Cell Carcinoma of the Oral Cavity Receiving Induction Chemotherapy with Cisplatin (CDDP), Docetaxel (TXT) and 5-Fluorouracil (5FU)

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Cisplatin-based neoadjuvant chemotherapy (NAC) has been reported to increase survival of patients with nasopharyngeal carcinoma, and organ preservation in those with laryngeal carcinoma, but its efficacy for other head and neck carcinomas is still controversial. We examined the effects of NAC for patients with stage III-IV squamous cell carcinoma of the oral cavity. The patients were divided into two groups; 9 patients who underwent NAC consisting of one course of cisplatin (CDDP), docetaxel (TXT) and 5-fluorouracil (5FU) followed by surgery (NAC group), and 18 patients who underwent surgery alone (control group). Complete response (CR) was not observed, but partial response (PR) was obtained in 6 of 9 patients (33%) of the NAC group. The 3-year survival rate was 29.6% in the NAC group and 81.5% in the control group. Although any valid conclusions could not be drawn because of the small number of patients examined here, NAC with CDDP, TXT and 5FU offered no advantages over standard treatment for advanced oral cancer in terms of survival.

INTRODUCTION

After introduction of cisplatin (CDDP) to cancer therapy in the early 1980's, CDDP-based neoadjuvant chemotherapy (NAC) has been widely used in the treatment of advanced head and neck squamous cell carcinoma (SCC) to achieve improvement of survival and organ preservation. Several randomized clinical trials showed that NAC increased survival of patients with nasopharyngeal SCC of advanced N stage by decreasing distant metastasis (1.9.13). NAC combined with radiotherapy was also reported to be of benefit to organ preservation in patients with T2-T3 laryngeal SCC in several randomized clinical trials (3.8.17).

On the other hand, the efficacy of NAC for head and neck SCC except nasopharngeal and laryngeal SCC is still controversial. Kohno et al. (11), Basu et al. (2), and Grau et al. (6) reported that NAC was useful for increasing survival rate of patients with oral SCC, while Kirita et al. (10), Giralt et al. (5), and Earle et al. (4) stated that NAC would be of benefit to preservation of organ function in those with locally advanced oral SCC. However, their results were based on uncontrolled clinical trials, so there was no evidence to support the results. Schuller et al. (15) and Mazeron et al. (12) showed no advantage of

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NAC for head and neck SCC in randomized clinical trials. Further, Hill et al. (7) reported no benefit of NAC for oral SCC by a historically-controlled study, and Okuta et al. (14) described that NAC was assosiated with a significant increase in regional failure for patients with stage II oral SCC by a historically-controlled study.

We recently performed NAC with CDDP, 5-fluorouracil (5FU), and docetaxel (TXT) for stage III-IV squamous cell carcinoma of the oral cavity. The aim of this study is to compare the prognosis of patients who underwent NAC to that of those who underwent surgery alone. Although the number of patients studied here was small and the results were from only a single institution, this is a controlled clinical trial on the efficacy of NAC for oral SCC.

PATIENTS AND METHODS

The subjects consisted of 27 patients with untreated, resectable, stage III-IV squamous cell carcinoma of the oral cavity treated at our hospital between 2001 and 2003. Among them, nine patients who were treated in 2002 underwent one course of NAC followed by surgery (NAC group), while 18 who were treated in 2001 and 2003 underwent surgery alone (control group). This study was approved by the ethics committee at Kobe University Graduate School of Medicine.

The regimen of NAC was shown in Fig. 1. Surgery was performed at 3 weeks after completion of the chemotherapy. Surgical margin was applied according to the extent of the initial tumor, that is, reduced operation was not performed even when good response was obtained by NAC.

Survival rate was calculated by the Kaplan-Meier method, and statistical analysis was carried out by the Generalized Wilcoxon Test.

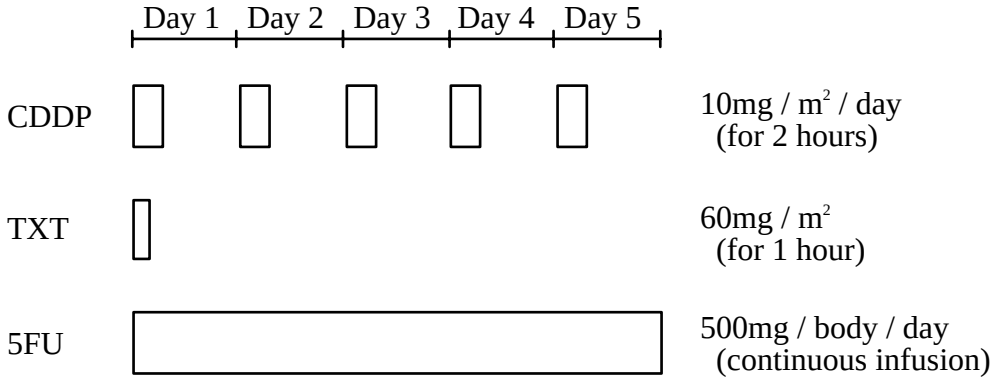

Fig. 1 Regimen of NAC with CDDP, TXT and 5FU.

RESULTS

1) Background factors of patients (Table 1)

The background factors of patients were summarized in Table 1. Twenty-seven patients consisted of 15 males and 12 females. The age of patients ranged from 31 to 82, with an average of 62.3 years old. The primary site in the NAC group was tongue in 6 patients and mandible in 3, while that in the control group was tongue in 7 patients, mandible in 7 and buccal mucosa in 4. Tumor cell differentiation of the NAC group was well in 5 patients and moderate in 4, while that of the control group was good in 10, moderate in 7 and poor in

1. In the NAC group, two were in stage III and 7 in stage IV, while in the control group, 4

Table 1 Background factors in the NAC and the control groups

Factors		NAC group*	Control group**	Total
Age (years)		50-74 (mean: 60.1)	31-82 (mean: 63.1)	mean: 62.3
Sex	Male:Female	6:3	9:9	15:12
Primary site	tongue	6	7	13
	mandible	3	7	10
	buccal mucosa	-	4	4
Histology	WDSCC	5	10	15
	MDSCC	4	7	11
	PDSCC	-	1	1
T stage	T1	1	-	1
	T2	-	5	5
	T3	2	4	6
	T4	6	9	15
N stage	N0	3	4	7
	N1	1	5	6
	N2	4	9	13
	N3	1	-	1
Stage	stage III	2	4	6
	stage IV	7	14	21
Total		9	18	27

*NAC group: Patinets who visited our hospital in 2002.

**Surgery group: Patients who visited our hospital in 2001 or 2003.

were in stage III and 14 in stage IV. There were no apparent differences in preoperative clinical factors between the NAC group and the control group.

2) Tumor response and toxicity of NAC (Table 2)

After one course of NAC, complete response (CR) was not observed, but partial response (PR) was obtained in 6 cases, while 2 patients were evaluated as no change (NC), and one as progressive disease (PD). The overall clinical response rate was 67%. The histological assessment showed various degrees of destruction of tumor structures as a result of chemotherapy. In five cases, there was severe destruction and a few tumor cells that were assessed as grade IIB according to the Oboshi & Shimosato classification (16). On the other hand, three cases, whose clinical response was PR in two and NC in one, were assessed as grade IIA because destruction was incomplete and many viable cells were observed, and one case whose clinical response was PD showed no destruction of tumor cells and was assessed as grade I.

Table 2 Tumor response and Grade 3-4 toxicity by NAC

Primary site (TNM)	Age	Side effect (grade)	Clinical response	Histological response**	Prognosis
tongue (T4N3M0)	50	N(3), A(3), D(3)	PR	IIB	3M dead of other cause
tongue (T1N2cM0)	61	A(3)	PR	IIB	5M dead of distant metastasis
tongue (T4N2bM0)	60	L(3), A(3)	NC	IIA	9M dead of local recurrence
mandible (T4N0M0)	61	-	NC	IIA	10M dead of local recurrence
mandible (T4N2bM0)	74	-	PD	I	11M dead of distant metastasis
tongue (T4N2cM0)	55	N(3), A(3)	PR	IIB	17M alive
tongue (T3N1M0)	54	N(3), N(3), A(3)	PR	IIA	20M dead of neck failure
tongue (T3N0M0)	67	L(4), N(3), T(3)	PR	IIB	29M alive
mandible (T4N0M0)	66	L(4), N(4)	PR	IIB	30M alive

* L=Leukopenia, N=Neutropenia, T=Thrombocytopenia, A=Alopecia, D=Diarrhoea

** Oboshi & Shimosato classification

Severe side effects of grade 3-4 were leukopenia, neutropenia, thrombocytopenia, alopecia and diarrhea. Alopecia occurred in 5 cases a few weeks after the start of chemotherapy. The nadirs of leukopenia and neutropenia were observed between days 6 and 10 but were manageable with granulocytes colony-stimulating factor (G-CSF). Thrombocytopenia and diarrhea were observed in only one case each. As mild side effect of grade 1-2, nausea (4 cases), vomiting (2 cases), and stomatitis and dizziness (one case each) were also found.

3) Treatment and prognosis according to treatment group

Table 3 shows treatment method and clinical course of patients in each group. All patients underwent tumor resection combined with neck dissection and reconstructive surgery. The methods of surgery were not different between the NAC and control groups. Postoperative radiotherapy was performed in 7 patients who had multiple metastatic lymph nodes. Although patients were divided into the two groups at random by the year of first visit, those in the NAC group showed more advanced pN stage than the control group.

Local recurrence was found in 3 patients of the NAC and one of the control groups, and the 3 of the NAC group could not be salvaged. Neck recurrence occurred in one patient of each group, in spite of final local cure. Two patients of each group developed distant metastasis in spite of loco-regional control.

The overall survival in the control group was 81.5% at 3 years. On the other hand, that in the NAC group was significantly lower, being 29.6% at 2 years ($p<0.05$) (Fig. 2). Three of 18 patients in the control group died (2 of distant metastasis and 1 of neck failure), while 6 of 9 in the NAC group died (2 of local disease, 2 of distant metastasis, 1 of neck failure, and 1 of other cause).

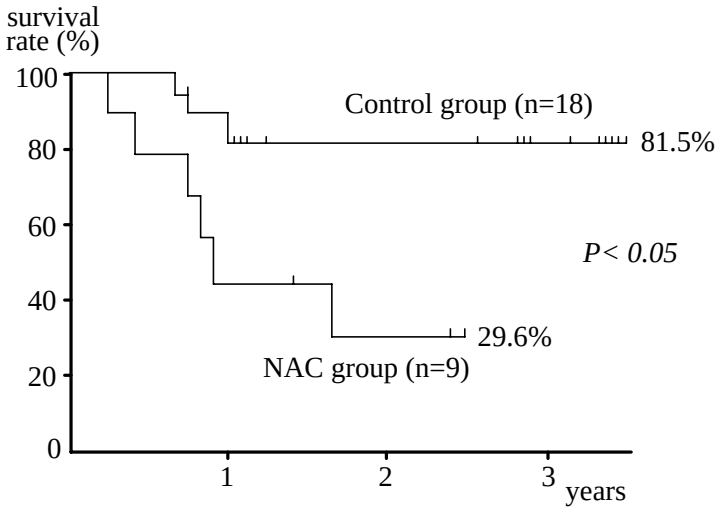

Fig. 2 Overall survival rate according to treatment group.

DISCUSSION

Although prognosis of oral cancer has been remarkably improved in recent years, patients with advanced tumor sometimes developed distant metastasis as well as local or neck recurrence and died of tumor. New treatment methods that prevent metastasis are, thus, necessary to achieve a better outcome in oral cancer patients.

Nishioka et al. reported that local control rate of patients with nasopharyngeal carcinoma did not differ between those who underwent NAC followed by radiotherapy and those who underwent radiotherapy alone, but 3-year survival rate in the former group was significantly higher than that of the latter group (13). International Nasopharynx Cancer Study Group reported that NAC benefited survival of patients with N2-3M0 nasopharyngeal carcinoma in randomized clinical trial (9). Al-Sarraf et al. also described that chemoradiotherapy increased survival of patients with advanced nasopharyngeal cancer in contrast to radiotherapy alone in a phase III randomized study (1).

The Department of Veterans Affairs Laryngeal Study Group showed in a controlled study that NAC plus radiation could preserve laryngeal function without decreasing survival rate, in contrast to surgery plus radiation, in patients with advanced, resectable laryngeal cancer (17). Clayman et al. reported that NAC plus radiotherapy could preserve the larynx in T2-3 laryngeal cancer in a controlled study, although T4 patients were recommended for surgery (3). Hong et al. also reported in a controlled study that the larynx could be preserved in patients with laryngeal cancer when they showed good response to NAC (8). Kohno et al. performed NAC with CDDP, VP-13 and MMC in 26 patients with advanced oral or pharynx carcinoma, and complete response (CR) was obtained in 8 and partial response (PR) in 14. They concluded that the regimen produced beneficial effect as an adjuvant therapy (11). Basu et al. attempted NAC consisting of different combinations of drugs in 44 patients with advanced oral cancer. The response rate was 89% (CR 25% and PR 64%), and they stated that chemotherapy was useful as an adjuvant therapy for oral cancer (2). Grau et al. also reported that cisplatin-based NAC showed a response rate of 80% (CR 13% and PR 67%) in 75 patients with stage III-IV oral cancer, and described that cisplatin-based NAC had a high response rate and low toxicity, and should increase survival

Table 3 Treatment and clinical course

	NAC group	Control group
Operation method		
tumor resection + neck dissection + reconstruction	9	18
others	0	0
Method of neck dissection		
radical neck dissection (RND)	3(2)	7(2)
functional neck dissection (FND)	6(4)	11(1)
Reconstructive surgery		
rectus abdominis	4(2)	5
forearm	2(2)	4
pectoralis major	2(2)	4(3)
fibula flap	1	4
latissimus dorsi	0	1
Number of positive lymph nodes		
0	3(1)	9(1)
1-2	1(1)	4
3-4	2(2)	5(2)
5-	3(2)	0
Postoperative radiotherapy		
performed	3(2)	4
not performed	6(4)	14(3)
Recurrence		
local recurrence	3(3)	1
neck failure (with local control)	1(1)	1(1)
distant metastasis (with loco-regional control)	2(2)	2(2)
Total	9(6)	18(3)

( ): dead patient

in oral cancer patients (6). Further, Kirita et al. (10), Giralt et al. (5), and Earle et al. (4) advocated that NAC possibly enabled less invasive surgery for oral cancer patients. However, these studies concluding that NAC could increase survival or decrease surgical damage in oral cancer patients were based on uncontrolled clinical trials, so there was no evidence to support the results.

On the other hand, there have been some reports that failed to show the efficacy of NAC for oral cancer. Schuller et al. (15) performed a randomized controlled trial. They divided

158 patients with advanced resectable head and neck squamous cell carcinoma into two groups; surgery and postoperative radiotherapy in 76 patients, and NAC, surgery and postoperative radiotherapy in 82 patients. The median survival time for conventional treatment was longer than the time for patients receiving NAC, although the survival time differences were not significant. They concluded that the final analysis demonstrated no benefit in survival using preoperative chemotherapy for advanced resectable head and neck cancer. Mazeron et al. (12) also conducted a randomized controlled trial in 131 patients with stage III-IV oral or pharynx cancer. The median survival was 22 months in patients who underwent NAC with CDDP, BLM, MTX and 5FU, while it was 29 months in the control group. They concluded that NAC did not offer any advantages over standard treatment. Further, Hill et al. (7) reported no benefit of NAC for oral SCC by a historically-controlled study, and Okuta et al. (14) described that NAC was associated with a significant increase in regional failure for patients with stage II oral SCC by a historically-controlled study.

We examined the effectiveness of NAC consisting of CDDP, 5FU and TXT for advanced resectable oral squamous cell carcinoma. Consequently, in spite of that the extent of resection was not reduced even when a good clinical response was obtained to NAC, local recurrence occurred more frequently in the NAC group. Further, the final outcome of the NAC group was significantly worse than that of the control group. The 3 patients of the NAC group who had local recurrence were evaluated as NC or PD with one course of induction chemotherapy, while 6 patients evaluated as PR obtained local control with surgery. These facts seemed to suggest that local tumor having less sensitivity to chemotherapy possibly invaded diffusely during NAC. However, the relationship between the response to NAC and local recurrence was not clear because the NAC group unexpectedly included patients with more advanced pN stage. We were going to perform this trial with a greater number of patients initially, but it was stopped since the prognosis was poor.

The main purposes of NAC are prognostic improvement and functional preservation. Although no valid conclusion can be drawn because of the small number of patients examined here, this study suggests that NAC with CDDP, TXT and 5FU may reduce the prognosis of oral cancer patients on the contrary. A large-scale randomized investigation is necessary in the future to evaluate the efficacy of NAC for oral cancer.

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