and neck cancer is lower, at 70 mg/m^2, compared with 100 mg/m^2 used in other countries. Secondly, some differences may be seen in the metabolism of steroids between ethnic groups.[4–7] As steroids are not indicated for antiemetic control in Japan, insufficient data are currently available related to their optimal dosing.

This study was conducted to measure the optimal dose of dexamethasone, in combination with the 5-HT$_3$ receptor antagonist granisetron, for antiemetic therapy during CDDP-containing chemotherapy for head and neck cancer in a Japanese patient population. Using a randomized crossover trial design, the efficacy and safety of 8 mg and 16 mg dexamethasone were assessed. Evaluated endpoints were the complete nausea and vomiting inhibition rate, the complete nausea inhibition rate, the complete vomiting inhibition rate, overall drug efficacy, degree of appetite loss, and side effects. The overall drug efficacy was assessed using criteria established by Suminaga et al.,[8] while the degree of appetite loss was measured by using version 2.0 of the National Cancer Institute common toxicity criteria (NCI-CTC).[9]

Subjects, materials, and methods

Subjects

The trial involved 36 adults (≤75 years of age) who were admitted to Yokohama City University Hospital and Yokohama City University Medical Center from May 2003 to December 2003 with stage III or IV advanced head and neck cancer. Each recruited patient was to receive two courses of CDDP-containing chemotherapy (CDDP, 60 mg/m^2 per day) every 4 weeks without pretreatment. All subjects consented to participate following a full explanation of the trial's objectives and content. The protocol was reviewed and approved by the ethics committee of the Yokohama City University School of Medicine and Yokohama Medical Center, Yokohama City University.

Exclusion criteria were: (1) concurrent illnesses such as severe heart disease, renal disease, and liver disease; (2) nausea and/or vomiting prior to treatment; (3) illnesses from which nausea and/or vomiting were a result, e.g., bowel obstruction, and peptic ulcer; (4) performance status (PS) of 4; (5) past history of hypersensitivity to drugs; (6) currently taking other antiemetic drugs and/or antipsychotic medication; (7) pregnant or possibly pregnant; and (8) deemed unsuitable by a doctor. In addition, patients who underwent radiation therapy or who experienced brain metastasis during the course of the trial were handled separately at the time of data analysis.

Design and treatment allocation

At the registration center, candidates were assessed for their suitability to participate in the trial and registered if deemed fit. The 36 participants (this number being settled upon by referring to a randomized crossover study for evaluating the antiemetic effect of the concomitant use of granisetron and dexamethasone against CDDP-induced delayed emesis in Japanese lung cancer patients)[10] were randomized by a hospital-based controller to two groups: the "dexamethasone 8 mg per day antecedent group" and the "dexamethasone 16 mg per day antecedent group" (Fig. 1). All patients received intravenous granisetron 3 mg 30 min before CDDP administration and 24, 48, and 72 h after CDDP administration in accordance with treatment regulations set by the Ministry of Health, Labour and Welfare of Japan. CDDP was intravenously administered for 3 h. The 8-mg antecedent group received 8 mg dexamethasone for course 1, switching to 16 mg for course 2. The 16-mg antecedent group received 16 mg dexamethasone for course 1, switching to 8 mg for course 2. The potential for carry-over effects between courses was minimized, if not eliminated, by a 3-week treatment-free interval between the two courses.

Dosage and administration

Dexamethasone 8-mg antecedent group

- Course 1: granisetron 3 mg + dexamethasone 8 mg were administered intravenously 30 min before CDDP administration and 24, 48, and 72 h after CDDP administration.
- Course 2: granisetron 3 mg + dexamethasone 16 mg were administered intravenously 30 min before CDDP administration and 24, 48, and 72 h after CDDP administration.

Dexamethasone 16-mg antecedent group

- Course 1: granisetron 3 mg + dexamethasone 16 mg were administered intravenously 30 min before CDDP administration and 24, 48, and 72 h after CDDP administration.
- Course 2: granisetron 3 mg + dexamethasone 8 mg were administered intravenously 30 min before CDDP administration and 24, 48, and 72 h after CDDP administration.

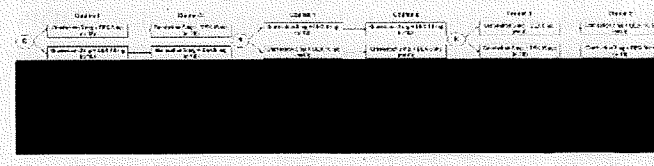

Fig. 1. Study design. The 36 participants were randomized to two groups: the "dexamethasone 8 mg per day antecedent group" and the "dexamethasone 16 mg per day antecedent group". All patients received intravenous granisetron 3 mg daily. The 8-mg antecedent group received 8 mg dexamethasone for course 1, switching to 16 mg for course 2. The 16-mg antecedent group received 16 mg dexamethasone for course 1, switching to 8 mg for course 2. *DEX*, Dexamethasone; *R*, randomization

Table 1. Criteria for judging antinausea effect and nausea grade

Judgment criteria (for each 8-h period)	
No. of points	
0	None (no symptoms)
1	Slight (nauseous, but can ingest liquids and solids)
2	Medium (nauseous, but can ingest liquids)
3	High (nauseous; cannot ingest liquids or solids)
Nausea grade	Sum total (0–24 h; no. of points)
A	0–3
B	4–6
C	7–9

Table 2. Efficacy criteria

Number of vomiting episodes during day 1	Nausea grade		
	A	B	C
≥5	Ineffective	Ineffective	Ineffective
3–4	Effective	Somewhat effective	Ineffective
1–2	Significantly effective	Effective	Somewhat effective
0	Significantly effective	Effective	Somewhat effective

Concomitant medication

Medicines thought to have an effect on the evaluation of the study drugs (e.g., other antiemetic drugs, antipsychotic drugs, and morphine) and those thought to have an effect on the digestive system were not given to the trial participants from the day before the trial commenced. In principle, during the trial, no additional doses of granisetron or other antiemetic therapies were used. However, in the case of extreme nausea and/or vomiting, the physician was allowed to administer treatment as he/she deemed necessary. In such cases, the results were considered to be "not valid".

Efficacy endpoints

Multiple physicians, nurses, and patients performed the following assessments, which were overseen by the first author. The assessment criteria were the same as those developed and used previously by Suminaga et al.[8]

A complete response (CR) was defined as no occurrence of nausea and zero instances of vomiting, including retching, following the administration of chemotherapy. Evaluation was performed 0–24 h after the administration of chemotherapy (day 1, acute phase) and separate assessments were made on days 2, 3, 4, and 5 (delayed phase).

The complete antinausea rate was defined as no nausea, and the complete vomiting inhibition rate was defined as the complete absence of vomiting. Each was evaluated 0–24 h after the administration of chemotherapy (day 1, acute phase) and on days 2, 3, 4, and 5 (delayed phase).

The degree of nausea for each 8-h period following the administration of chemotherapy was scored according to predetermined efficacy criteria (Table 1). The sum total for the nausea experienced during the 24-h period following the administration of chemotherapy (day 1) was broken down into three levels: grades A, B, and C (Table 1). The nausea grade, together with the number of instances of vomiting during day 1, was used as the basis for evaluating overall antiemetic efficacy, according to the predetermined efficacy criteria (Table 2). There were four levels of efficacy: "significantly effective", "effective", "somewhat effective" and "ineffective". The overall efficacy rate was defined as the percentage of patients in whom the treatment was assessed as "significantly effective". Evaluation was performed on days 2–5 in the same way as the evaluation of the other study parameters was done.

Table 3. Degree of appetite loss (NCI-CTC version 2.0)[9]

0	Almost no change
1	Appetite halved
2	Appetite 1/3 of that before treatment
3	Almost unable to eat
4	Other

Degree of appetite loss

Degree of appetite loss was evaluated according to NCI-CTC version 2.0[9] (Table 3), comparing the condition of the patient 24 h prior to receiving chemotherapy and the condition of the patient for each 24-h period following the administration of chemotherapy.

Adverse events

Both subjective and objective findings discovered during the trial were recorded and their connection with the trial medication investigated.

Data analysis

Each assessment item was evaluated at the time of administration of dexamethasone 8 mg and 16 mg. The results obtained from the two treatment groups were compared using Fisher's exact test and evaluated at a 5% significance level.

Results

Patient characteristics

Of the 36 patients, divided at random into an 18-person 8-mg dexamethasone antecedent group and an 18-person dexamethasone 16-mg antecedent group, each showed sufficient response for efficacy to be analyzed. Data in Table 4 show that the patient groups were well balanced in terms of baseline characteristics. All patients completed the crossover, and CDDP dose reduction was not required for any patient during chemotherapy course 2. There was also no case of extreme nausea and vomiting such that additional treatment became necessary. There were also no cases of brain metastases.

Complete response (CR) rates

The CR rate for day 1 (acute phase) was 58.3% for the 8-mg dexamethasone group and 63.8% for the 16-mg group ($P = 0.8092$). Separate assessments were made on each day between days 2 and 5. For day 2, the results for the two groups were 36.1% and 52.7%, respectively ($P = 0.2355$); the results were 33.3% and 38.8% ($P = 0.8065$) for day 3; 22.2% and 25.0% ($P = 1.00$) for day 4; and 22.2% and 27.8% ($P = 0.786$) for day 5. At any given time, no statistically significant difference in CR rates was found between the dosages (Fig. 2).

Complete antinausea rate and complete vomiting inhibition rate

The complete antinausea rate for day 1 (acute phase) was 58.3% for the 8-mg dexamethasone group and 66.7% for 16-mg group ($P = 0.6268$). For day 2, the results were 36.1% and 52.7%, respectively ($P = 0.2355$); the results were 33.3% and 44.4% ($P = 0.4687$) for day 3; 22.2% and 27.7% ($P = 0.861$) for day 4; and 22.2% and 27.8% ($P = 0.786$) for day 5. At any given time, no significant difference in the

Table 4. Patient characteristics

	Dexamethasone 8-mg antecedent ($n = 18$)	Dexamethasone 16-mg antecedent ($n = 18$)
Sex		
Male	13	15
Female	5	3
Performance status		
0	17	16
1	1	2
Primary site		
Nasopharyngeal cancer	3	3
Oropharyngeal cancer	1	4
Hypopharyngeal cancer	6	5
Orohypopharyngeal cancer	1	–
Maxillary cancer	3	1
Maxillary sinus cancer	1	–
Gum cancer	1	1
Laryngeal cancer	1	2
Parotid cancer	–	1
Unknown	1	1
Chemotherapy history		
Yes	1	1
No	15	15
Unknown	2	2
Chemotherapy		
Course 1		
CDDP+5-FU+LV+MTX	14	15
CDDP+5-FU+TXT	2	2
CDDP+TS-1	1	–
CDDP+5-FU+LV	1	–
CDDP+5-FU	–	1
Course 2		
CDDP+5-FU+LV+MTX	15	16
CDDP+5-FU+TXT	2	2
CDDP+TS-1	1	–

CDDP, cisplatin; 5-FU, fluorouracil; LV, leucovorin; MTX, methotrexate; TXT, docetaxel; TS-1

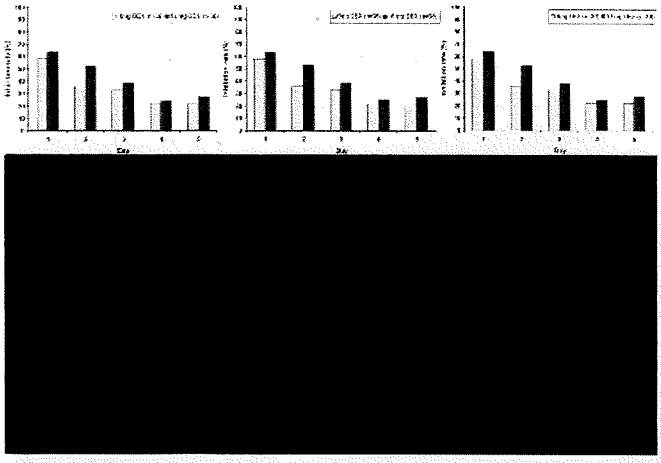

Fig. 2. Complete response (CR) rates. CR was defined as no occurrence of nausea and zero instances of vomiting following the administration of chemotherapy. Evaluation was performed 0–24 h after the administration of chemotherapy (day 1; acute phase) and separate assessments were made on days 2, 3, 4, and 5 (delayed phase)

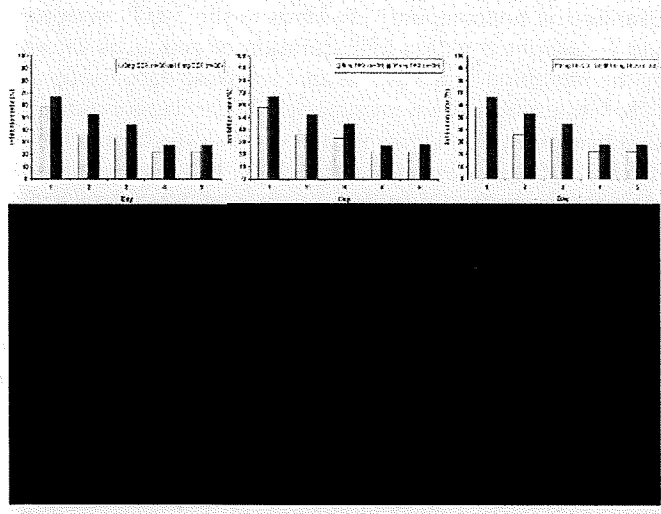

Fig. 3. Complete antinausea rate. Complete antinausea was defined as no nausea. Each patient was evaluated 0–24 h after the administration of chemotherapy (day 1; acute phase) and on days 2, 3, 4, and 5 (delayed phase)

complete antinausea rate was found between the dosages (Fig. 3).

The complete vomiting inhibition rate for day 1 (acute phase) was 100.0% for the 8-mg dexamethasone group and 91.7% for the 16-mg group (P = 0.2394). For day 2, the results were 80.6% and 83.3%, respectively (P = 1.00); the results were 72.2% and 72.2% (P = 1.00) for day 3; 44.4% and 55.5% (P = 0.4798) for day 4; and 36.1% and 50.0% (P = 0.341) for day 5. At any given time, no significant difference in the complete vomiting inhibition rate was found between the dosages (Fig. 4).

Overall efficacy rates

Equivalent high levels of efficacy were found for both dexamethasone dosages during day 1: overall efficacy rates were

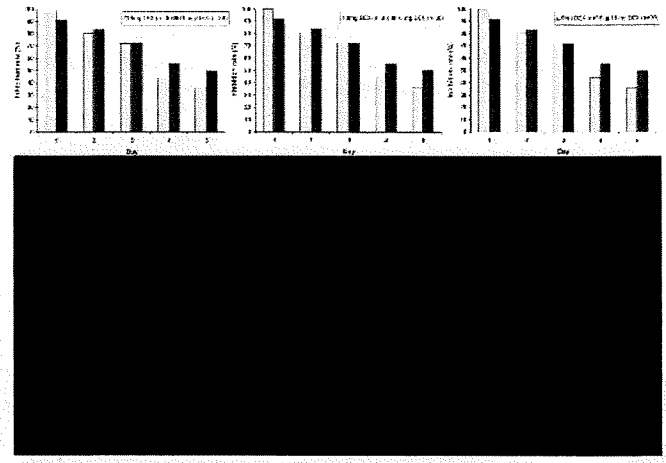

Fig. 4. Complete vomiting inhibition rate. Complete vomiting inhibition was defined as the complete absence of vomiting. Each patient was evaluated 0–24 h after the administration of chemotherapy (day 1; acute phase) and on days 2, 3, 4, and 5 (delayed phase)

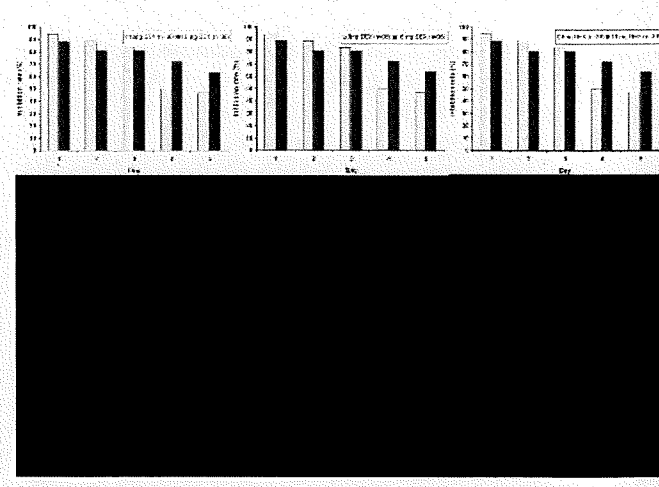

Fig. 5. Overall efficacy rate. The nausea grade (calculated as shown in Table 1), together with the number of instances of vomiting during day 1, was used as the basis for evaluating overall antiemetic efficacy, according to the predetermined efficacy criteria (shown in Table 2). There were four levels of efficacy: "significantly effective", "effective", "somewhat effective", and "ineffective". The overall efficacy rate was defined as the percentage of patients in whom the treatment was assessed as "significantly effective". Evaluation was performed on days 2–5 in the same way as the evaluation of the other study parameters was done

94.4% at 8 mg and 88.8% at 16 mg (P = 0.7637). For day 2, the results were 88.9% and 80.6%, respectively (P = 0.514); the results were 83.3% and 80.5% (P = 1.00) for day 3; 50% and 72.2% (P = 0.898) for day 4; and 47.2% and 63.9% (P = 0.235) for day 5. At any given time, no significant difference was found between the dosages (Fig. 5).

Degree of appetite loss

Table 5 shows the inhibitory effect of the treatment on appetite loss, as the percentage of patients who were evaluated as showing "0; almost no change in appetite" based on NCI-CTC version 2.0.[9] At any given time, no significant

Table 5. Inhibitory effect on appetite loss (days 1–5)

Days after administration	Number of patients reporting grade 0 appetite loss (%)		*P* value
	8 mg DEX (n = 36)	16 mg DEX (n = 36)	
Day 1	17 (47.2)	19 (52.8)	0.8139
Day 2	11 (30.6)	16 (44.4)	0.3303
Day 3	10 (27.8)	14 (38.9)	0.4537
Day 4	7 (19.4)	9 (25.0)	0.7775
Day 5	8 (22.2)	9 (25.0)	1.0

DEX, dexamethasone

difference was found between the 8-mg and 16-mg dosage groups in the rates of patients reporting "almost no change in appetite".

Adverse events

At the time of 8-mg dexamethasone administration, two cases of *Herpes zoster* infection were observed; and at the time of 16-mg dexamethasone administration one case of elevated blood glucose was observed. These were not severe, and their causal relationship with the administered drugs was equivocal.

Discussion

A study conducted in 1983 to identify and rank the symptoms experienced by patients receiving cancer chemotherapy reported that vomiting and nausea were the most severe symptoms experienced.[11] However, the advent of new antiemetic regimens and changes in cancer chemotherapy have resulted in a reduction of the severity of some symptoms patients have experienced while receiving chemotherapy. In 1993, nausea was reported as the most severe symptom, followed by fatigue and alopecia. Vomiting, which was the most severe symptom in 1983, was ranked fifth in 1996.[12] Therefore, while recent progress has been remarkable, CINV remains a significant problem for patients and is associated with a substantial deterioration in quality of life. As evidenced by the present study and other recent studies (for example, Vardy et al. [2006][13]; Ikeda et al. [2005][14]; Abali et al. [2005][15]; and Gralla et al. [2005][16]), work to develop and optimize anti-CINV regimens is ongoing.

Cisplatin (CDDP) is one of the most highly emetogenic agents, with doses of 50 mg/m^2 or more inducing nausea and vomiting within 24 h in more than 90% of patients not administered antiemetic prophylaxis. Even in those patients receiving appropriate prophylaxis during multiple-cycle chemotherapy, the risk of vomiting associated with CDDP is 20% greater than that with regimens that do not contain CDDP.[17]

In recent years it has become clear that receptors for serotonin (5-hydroxytryptamine; 5-HT), specifically the 5-HT_3 receptor, contribute to CINV. Granisetron strongly and selectively binds to the 5-HT_3 receptor with a binding constant of 0.26 nM and exhibits a 4000–40 000 times greater binding affinity for the 5-HT_3 receptor than other binding sites, including other 5-HT subtypes and adrenergic, histaminergic, and opioid receptors. Its selectivity for the 5-HT_3 receptor over other receptor types is more than 1000: 1. Granisetron noncompetitively binds to the 5-HT_3 receptor and is associated with a long duration of action, as shown by the inhibition of a 5-HT axonal response flare for up to 24 h. Granisetron is unique among 5-HT_3-receptor antagonists because it is not metabolized via the cytochrome P450 (CYP) 2D6 pathway and is, therefore, less susceptible to variation in patient response because of factors such as pharmacogenomic differences.[18] The proven effectiveness of granisetron in CINV makes it a valuable alternative in combating this extremely unpleasant symptom.

Drugs such as granisetron have made it possible to control nausea and vomiting during the acute phase of chemotherapy, and chemotherapy compliance has dramatically improved as a result. However, the efficacy of these drugs against CINV in the delayed phase is notably reduced compared with that during the acute phase. It is often reported that steroids used in combination with 5-HT_3 receptor antagonists extend the antiemetic effect, offering control of delayed nausea and vomiting.[1,2] However, in Japan, detailed studies on the utility and appropriate dosing of steroids as antiemetics have not been conducted. Also, the doses of CDDP used for treating head and neck cancer in Japan differ from those used in other countries, making the direct use of the antiemetic steroid doses recommended in other countries inappropriate for Japanese patients.

The present study combined the most commonly used 5-HT_3 receptor antagonist in Japan, granisetron, with the steroid, dexamethasone. In this combination, the safety and antiemetic efficacy of 8 mg and 16 mg dexamethasone were examined in a randomized crossover trial. Following the administration of chemotherapy, the CR – defined as no nausea and zero instances of vomiting – during the period of 0 to 24 h following chemotherapy (acute phase) was 58.3% for an 8-mg dose of dexamethasone and 63.8% for a 16-mg dose (P = 0.8092). Both of these are high inhibition rates, and similar results were seen for days 2–5. In addition, the overall efficacy rates for both doses were exceptionally high – approximately 90% during day 1 and maintaining an overall efficacy rate of 80% or higher until day 3.

Because NK-1 antagonists were under development at the time of conducting this trial, we could not evaluate the effects of a combination, of granisetron and dexamethasone with an NK-1 antagonist on acute and delayed nausea and vomiting induced by CDDP-containing chemotherapy for head and neck cancer. The results of a phase 2 clinical study conducted in Japan to evaluate the concurrent use of an NK-1 antagonist (aprepitant) and a 5-HT_3 antagonist (granisetron) for controlling CINV showed equivocal efficacy compared with data obtained in other countries (data have not been published). Therefore, a combination containing an NK-1 antagonist, a 5-HT_3 antagonist, and dexamethasone is expected to become the regimen used to control CINV in Japan.

In the present study, for endpoints other than than CR (e.g., complete antinausea rate, complete vomiting inhibition rate, and degree of appetite loss), 3 mg granisetron in combination with 8 mg dexamethasone was equivalent in efficacy to 3 mg granisetron in combination with 16 mg dexamethasone. However, from the fourth day after the completion of antiemetic therapy, the positive effects on nausea and vomiting tended to decrease. This suggests that it is desirable to continue antiemetic therapy for as long as necessary in order to control nausea and vomiting. No side effects were observed for either dose of dexamethasone or for granisetron. The significance of our data will be evaluated in a larger study in order to help optimize appropriate antiemetic strategies and enhance quality of life in patients undergoing highly emetogenic chemotherapy.

Conclusion

In summary, data from this study demonstrate that the steroid dexamethasone and the 5-HT3 receptor antagonist granisetron, when used in combination, effectively control both acute and delayed nausea and vomiting associated with CDDP-containing chemotherapy for head and neck cancer. The results also suggest that the efficacies of 8 mg (low-dose) dexamethasone and 16 mg (standard-dose) dexamethasone are almost equal. The combination therapy of dexamethasone and granisetron was able to safely and effectively control CINV. From the standpoint of making a complete treatment plan and improving a patient's quality of life, we conclude that this combination therapy is an effective antiemetic treatment that encompasses both the acute and delayed phases of CINV.

Conflict of interest statement

No author has any conflict of interest.

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ORIGINAL ARTICLE

Randomized controlled phase II comparison study of concurrent chemoradiotherapy with docetaxel, cisplatin, and 5-fluorouracil versus CCRT with cisplatin, 5-fluorouracil, methotrexate and leucovorin in patients with locally advanced squamous cell carcinoma of the head and neck

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Abstract We compared concurrent chemoradiotherapy (CCRT) with docetaxel, cisplatin (CDDP), and 5-fluorouracil (5-FU) (TPF) with CCRT with CDDP, 5-FU, methotrexate and leucovorin (PFML) in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) in terms of safety and efficacy on survival. A total of 100 patients were enrolled. The TPF group received CCRT with the TPF regimen [docetaxel (50 mg/m^2: day 1), CDDP (60 mg/m^2: day 4), and continuous 5-FU infusion (600 mg/m^2/day: days 1–5)]. In the PFML group, patients received CCRT with the PFML regimen [CDDP (60 mg/m^2: day 4)], continuous 5-FU infusion (600 mg/m^2/day: days 1–5), methotrexate (30 mg/m^2: day 1) and leucovorin (20 mg/m^2/day: days 1–5)]. Both groups received 2 cycles of chemotherapy during definitive radiotherapy. The total radiation dose was between 66.6 and 70.2 Gray. The overall response rates after CCRT were 98 with 90% of a pathologically complete response (pCR) in the TPF group and 94 with 77% in the PFML group. For grade 3/4 adverse events, mucositis was more frequent in the PMFL group, and the TPF group showed a higher incidence of hematological toxicity. CCRT with TPF or PMFL for advanced SCCHN was tolerable and produced excellent survival rates.

Keywords Concurrent chemoradiotherapy · Cisplatin · Docetaxel · 5-Fluorouracil · Squamous cell carcinoma of the head and neck (SCCHN)

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Introduction

Squamous cell carcinoma of the head and neck (SCCHN) is the most common malignant tumor in this site [1]. Two-thirds of patients present with locoregionally advanced lesions (T3 or T4) and/or regional lymph node involvement (N1–N3). The 5-year survival rates are <30% despite radical surgery and/or radiotherapy (RT) [2, 3]. During the past 20 years, combined modality approaches have been developed to enhance locoregional disease control, reduce distant metastases, and improve survival in patients with advanced SCCHN. Multidisciplinary treatment including chemotherapy with antitumor activity when used alone, or radiosensitizing effects when combined with RT, has been employed to improve patient outcome. Systematic reviews using meta-analysis have revealed that chemotherapy given concurrently with RT (CCRT) shows a significant benefit for the survival rate of patients with SCCHN compared with RT alone [2, 4, 5].

Regimens that include cisplatin (CDDP) and 5-fluorouracil (5-FU) (PF) are currently considered standard chemotherapy for patients with locally advanced SCCHN. A recent systematic review using meta-analysis revealed that the docetaxel plus PF (TPF) regimen shows a significant benefit for the survival rate of patients with SCCHN compared with the PF regimen in neoadjuvant chemotherapy

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(NAC) setting studies [6]. Recently, NAC with TPF followed by RT has been shown to be more efficacious than the PF regimen in terms of survival for advanced SCCHN [7, 8].

Based on CCRT integration studies, CCRT is one of the standard treatment modalities for the definitive treatment of locoregionally advanced SCCHN, particularly resectable advanced cases, to preserve function while maintaining or improving locoregional control and survival rates [9, 10]. We have also examined the safety and effectiveness of TPF in the NAC setting [11]. Furthermore, we have described CCRT with TPF [12, 13] and showed that this regimen was better than NAC with TPF followed by definitive RT in terms of survival rate, although the overall response rate (ORR) and pathologically complete response (pCR) rates were similar in different treatment modalities [14].

Since 1995, we have developed multiagent PFML chemotherapy consisting of PF with methotrexate (MTX) and leucovorin (LV) for locoregionally advanced SCCHN [15–17]. MTX and LV are modulators of the antitumor actions of 5-FU. PFML had initially been used in the NAC setting study. From the end of 1998, PMFL has been applied to improve locoregional control and the survival rates of patients with advanced SCCHN [15, 16] and to preserve function in the CCRT modality [17].

Here, we compared CCRT with TPF and CCRT with PFML in patients with locally advanced SCCHN. The main endpoints of this phase II study were to evaluate the response rates and toxicities of each CCRT modality and to obtain a preliminary assessment regarding the efficacy of both regimens.

Patients and methods

Patient population

Patients were included if they had histologically or cytologically confirmed SCCHN, at least one dimensionally measurable lesion, and stage III or IV disease without evidence of distant metastases according to the 2002 staging system of the Union Internationale Contre le Cancer. Patients with the oropharynx, hypopharynx, larynx, oral cavity or paranasal sinus as the primary sites were eligible. Resectable cases were enrolled; however, patients with invasion to the prevertebral muscle, common or internal carotid artery (i.e., those showing positive results on the artery occlusion test), or bulky metastasis in the retropharyngeal lymph nodes were excluded. Patients who had received previous chemotherapy, RT or surgery were excluded; those with another cancer were ineligible.

Patients must be from 20 to 75 years of age and meet the following criteria: an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; life expectancy of at least 3 months; WBC count $\geq$ 4,000 cells/μl; absolute neutrophil count (ANC) $\geq$ 2,000 cells/μl; platelet count $\geq$ 100,000/μl; hemoglobin level $\geq$ 9.5 g/dl; AST, ALT and alkaline phosphatase levels below 2.5 times the upper limit of normal (ULN); total bilirubin and creatinine levels lower than 1.5 times the ULN, BUN level below the ULN; and 24-h creatinine clearance rate > 65 ml/min. Patients with significant cardiac arrhythmia or heart failure were ineligible. All patients provided written informed consent prior to enrollment. This study had been approved by the institutions' institutional review board.

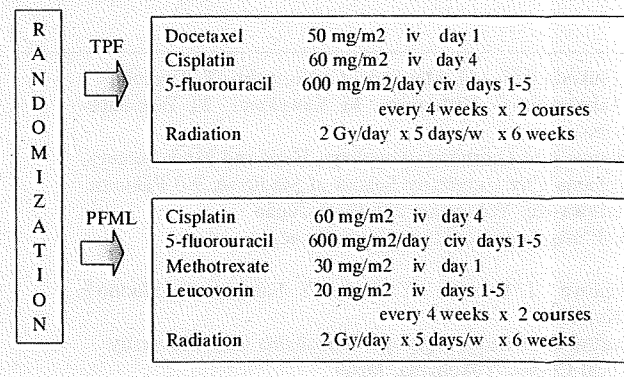
Treatment schedule

From our phase I study of the TPF regimen [12], docetaxel (50 mg/m^2) was administered intravenously over 1 h on day 1. More than 1 h after completion of the intravenous docetaxel, 5-FU (600 mg/m^2/day) on days 1 through 5 was administered by continuous intravenous infusion with 3.5 l of normal saline per day. CDDP (60 mg/m^2) was administered intravenously on day 4. The PFML regimen consisted of a combination of 4 drugs: cisplatin (60 mg/m^2: day 4), 5-FU (600 mg/m^2/day: days 1–5), MTX (30 mg/m^2: day 1), and LV (20 mg/m^2/day: days 1–5) [15–17] (Table 1).

Two cycles of each regimen were administered every 4 weeks during RT. Patients received ramosetron (0.3 mg) and dexamethasone (8 mg) intravenously on days 4 through 8 of chemotherapy in each cycle.

Re-treatment on day 29 required the following: ANC $\geq$ 2,000 cells/μl; platelet count $\geq$ 100,000/μl; hemoglobin level $\geq$ 9.5 g/dl; AST, ALT and alkaline phosphatase levels below 2.5 times the ULN; 24-h creatinine clearance rate > 60 ml/min; and resolution of all other nonhematological toxicities (except alopecia, musculoskeletal pain and fatigue) to be baseline or less than Grade 1. If there were some toxicities as described earlier,

Table 1 Study design



cycle 2 chemotherapy was delayed, and if the delay exceeded 14 days, the patient was removed from the study.

RT was performed 5 days a week with a single daily fraction of 1.8 or 2.0 Gray (Gy) using 6 MV X-ray linear accelerators. After a total dose of 36–40 Gy with the first course of each regimen, all patients were clinically re-evaluated by endoscopy and computed tomography (CT) or magnetic resonance imaging (MRI). Patients with a 50% or greater decrease in the product of 2 perpendicular diameters of the primary and neck tumor continued RT with a second course of chemotherapy and completed RT up to a total dose of 66.6–70.2 Gy. For nonresponders, definitive surgery was recommended.

Every effort was made to continue radiation on schedule. Subcutaneous granulocyte colony-stimulating factor (G-CSF; 100 μg/day) was injected if the neutrophil count was <1,000 cells/μl after CCRT. When Grade ≥ 3 toxicities were observed and persisted for more than 7 days, the second cycle of chemotherapy was delayed for about 7 days. If the severe toxicities continued for more than 14 days, radiation alone was delivered and CCRT was discontinued. When patients could not eat and drink foods because of oral or pharyngeal pain induced by CCRT, a gastric tube was inserted to maintain patients' nutritional condition.

Endpoints, clinical response, and further treatment

The primary endpoints were overall response rate (ORR) and pCR rate. The secondary endpoints were overall survival (OS), relapse free survival (RFS), and adverse events (AE). The clinical response was assessed for each patient according to the combined findings of CT, MRI and ultrasonic examinations 4–6 weeks after CCRT completion. The definitions of CR, partial response (PR), no change (NC) and progressive disease (PD) were based on the standard definitions established by WHO [18]. To evaluate pCR, responses to CCRT were confirmed by biopsies of the primary site in all cases. For N1–N3 lymph node disease, ultrasound-guided fine needle aspiration cytology (FNAC) of the neck lymph nodes was performed. Responses at the primary site and the regional nodes were scored separately, and the OR was based on the worst of the two responses. Surgery of the primary tumor site was recommended for patients who failed to achieve pCR after CCRT completion. Surgery was performed routinely 6–8 weeks after CCRT completion.

Toxicity assessment

Toxicity was assessed once per cycle according to the 2003 Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0). Resolution of side effects [e.g., myelosuppression, mucositis, fever (>38.0°C)] and other disorders was required prior to initiating the second treatment cycle. A dose-limiting toxicity (DLT) was defined as Grade 4 mucositis that interrupts treatment for more than 2 weeks, Grade 4 thrombocytopenia, Grade 2 nephrotoxicity, or Grade 3 or 4 nonhematologic toxicity, excluding alopecia, nausea, vomiting, anorexia and fatigue. Grade 4 neutropenia, which was predicted to occur in most patients, was not considered a DLT, because it could be clinically managed by G-CSF support.

Statistical analysis

The two-tailed t test was used to analyze independent groups and the X^2 test for associations. A finding was considered significant if $P < 0.05$. OS and RFS rates were estimated according to the Kaplan–Meier product limit method [18].

Results

Patients

From September 2003 to December 2007, we enrolled 100 patients all of whom were randomized. Three patients refused treatments after registration, and 1 received a different RT method. These 4 patients were excluded from this study; 48 patients were evaluable for response and safety in each group. The baseline patient characteristics of those evaluable for response are shown in Table 2. The characteristics of the patients were well balanced between the two groups.

Eighty patients were male and 16 were female, and the average age was 62.0 years (range, 36–74 years) with 36 patients over 65 years of age. The PS (ECOG) of all the patients was 0. The primary disease sites were the oral cavity ($n = 7$), maxillary sinus ($n = 9$), oropharynx ($n = 28$), hypopharynx ($n = 30$), and larynx ($n = 22$). Thirty-one patients (32%) had T3, and 28 patients (29%) had T4 primary tumors. Thirty-six patients had stage III disease, and the remaining 60 patients had stage IV (63%). Among the 96 patients, 19 had N_1 (20%), 50 (52%) had N_2 and 1 had N_3 (2%).

Responses and survival

In 4–6 weeks after RT completion, all patients underwent biopsies of the primary tumor and/or FNAC of neck lesions to determine the pathological response.

One patient with hypopharyngeal carcinoma (T4N2b) showing NC at 40 Gy with one course of PFML received definitive surgery. The remaining 97 patients were

Table 2 Patients' characteristics

	TPF ($n = 48$)	PFML ($n = 48$)
Age (years)		
Median (range)	62 (36–73)	62 (39–74)
>65 years	19 (40%)	15 (31%)
Gender		
Male	40 (83%)	40 (83%)
Female	8 (17%)	8 (17%)
PS (ECOG)		
0	48 (100%)	48 (100%)
1	0 (0%)	0 (0%)
Primary site		
Oral cavity	6 (13%)	1 (2%)
Maxillary sinus	5 (10%)	4 (8%)
Oropharynx	14 (29%)	14 (29%)
Hypopharynx	12 (25%)	18 (38%)
Larynx	11 (23%)	11 (23%)
Clinical stage		
III	19 (40%)	17 (35%)
IV	29 (60%)	31 (65%)
T		
1	5 (10%)	2 (4%)
2	14 (29%)	16 (33%)
3	15 (32%)	16 (33%)
4	14 (29%)	14 (29%)
N		
0	15 (32%)	11 (23%)
1	10 (21%)	9 (19%)
2a	1 (2%)	2 (4%)
2b	17 (35%)	17 (35%)
2c	4 (8%)	9 (19%)
3	1 (2%)	0 (0%)

administered at least one course of chemotherapy with definitive RT. Thirty-seven of 48 patients (77.1%) in the PFML group and 39 of 48 patients (81.3%) in the TPF group received planned CCRT. The second course of chemotherapy was discontinued in 11 patients in the PFML group because of renal toxicity (5 patients), chronic neutropenia (5 patients), and no response to CCRT (the case mentioned earlier). On the other hand, the second course was discontinued in 9 patients in the TPF group because of chronic neutropenia (5 patients), renal toxicity (3 patients), and hepatic toxicity (1 patient).

In the group given CCRT with TPF, the ORR was 98% (47/48) and the pCR rate was 90% (43/48), whereas in the group given CCRT with PFML, the ORR was 94% (45/48) and the pCR rate was 77% (37/48) (Table 3).

After or during the CCRT, 6 of 11 patients showing PR or NC in the PFML group and 4 of 5 patients showing PR or NC in the TPF group received curative operation. Other 6 patients with remnant tumors refused operation.

After a median follow-up of 930 days (range, 214–1,510 days), the 1-year, 2-year, and 3-year OS rates in the PFML group were 90.0, 88.0, and 83.8%, and the 1-year, 2-year, and 3-year RFS rates in the PFML group were 76.5, 73.3 and 73.3%, respectively (Figs. 1, 2). On the other hand, the 1-year, 2-year, and 3-year OS rates in the TPF group were 100, 95.8 and 95.8%, and the 1-year, 2-year, and 3-year RFS rates in the TPF group were 93.0, 81.6, and 77.4%, respectively.

Regarding recurrence in CR cases, 6 (14.0%) of 43 patients in the TPF group relapsed (i.e., 1 case in the local site, 1 in the neck and 4 in the lung with the primary site relapse). On the other hand, 10 (27.0%) of 37 patients in the PFML group relapsed (i.e., 4 cases in the primary site, 2 in the neck and 4 in the distant lesions) including 1 patient with primary site relapse (Table 4). All patients with recurrence excluding cases with distant metastases underwent salvage surgery.

Toxicity

There were no deaths resulting from treatment in this study. Tables 5 show the toxicities in each group. In the group administered CCRT with the TPF regimen,

Table 3 Response ($n = 96$)

Chemotherapy and CRT	TPF ($n = 48$)	PFML ($n = 48$)	*P*
Overall RR (95% CI)	98% (88.9–99.9)	94% (82.8–98.7)	0.31
Complete RR (95% CI)	90% (77.3–96.5)	77% (62.7–88.0)	0.10

	CR	PR	NC	PD	NE
TPF	43 (90%)	4	1	0	0
PFML	37 (77%)	8	2	0	1[a]

[a] Surgery was performed because of a nonresponder CCRT at the dose of 40 Gy

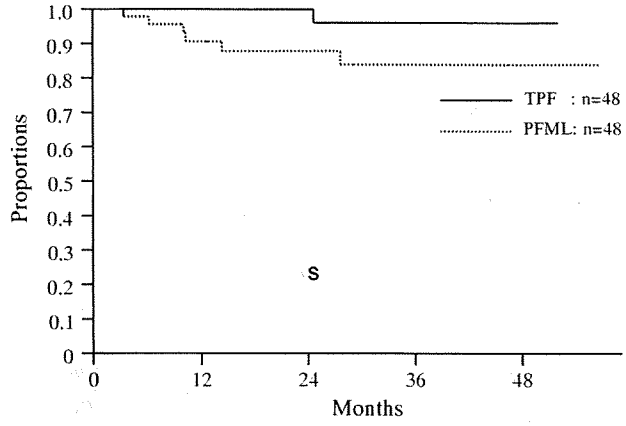


Fig. 1 Kaplan–Meier overall survival curves. The 3-year overall survival rates were 83.8% in the PFML group and 95.8% in the TPF group

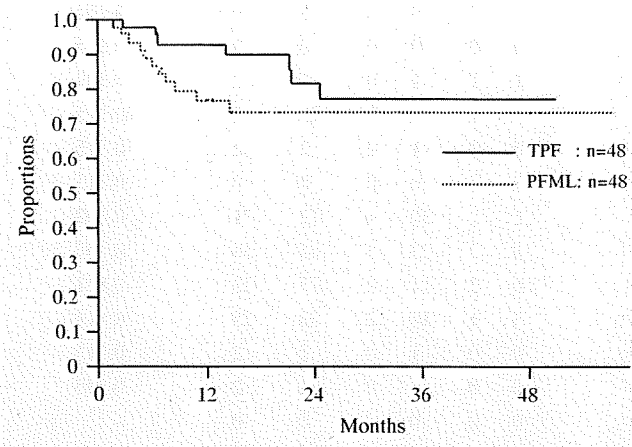


Fig. 2 Kaplan–Meier relapse-free survival curves. The 3-year relapse-free survival rates were 73.3% in the PFML group and 77.4% in the TPF group

leukocytopenia was the most common and severe AE observed as Grade 3 ($n = 26$) and 4 ($n = 7$). Moreover, Grade 3 and 4 neutropenia was observed in 33% (33/48). There was a significant difference in Grade 3 and 4 neutropenia and leukocytopenia between the two groups. The next frequent and severe adverse events were mucositis and dermatitis similar to the PFML group. In the PFML group, the most common AE was Grade 3 ($n = 30$) and 4 ($n = 4$) mucositis. The next severe toxicity was dermatitis associated with CCRT showing 58% of Grade 3 and 4. In terms of Grade 3 and 4 mucositis, a significant difference was found between the two groups. Patients with Grade 3 and 4 mucositis required a feeding tube for nutritional support (77% in the PFML group and 54% in the TPF group).

To date, late AEs (e.g., swallowing disturbance and pharyngeal stenosis) have not been observed.

Table 4 Sites of recurrence in CR cases

	Primary site	Site of recurrence	Days
TPF	Oropharynx	Lung	653
	Hypopharynx	Local, lung	364
	Hypopharynx	Neck lymph node	431
	Larynx	Local, lung	83
	Larynx	Local	197
	Larynx	Lung	203
PFML	Oral cavity	Neck lymph node	75
	Oropharynx	Neck lymph node	77
	Oropharynx	Local	225
	Oropharynx	Lung, bone, skin	258
	Hypopharynx	Lung, liver	180
	Hypopharynx	Local, lung	200
	Hypopharynx	Lung	444
	Larynx	Local	49
	Larynx	Local	160
	Larynx	Local	334

Discussion

CCRT has been thought to be an effective treatment modality for resectable SCCHN in terms of good outcome and function preservation. However, CCRT with a single agent (particularly CDDP) has been mostly applied to several phase III studies [9, 10, 19–21]. The use of multiagent CCRT including CDDP appears to be more efficacious than CCRT with CDDP alone. Several studies regarding multiagent CCRT including CDDP plus 5-FU have also been reported. Adelstein et al. [22] reported a retrospective review with long-term follow-up of 222 patients receiving CCRT with 4-day continuous infusions of 5-FU (1,000 mg/m^2/day) and CDDP (20 mg/m^2/day) during weeks 1 and 4. The total RT dose was either 68 or 72 Gy. The 5-year local control rate without surgical resection was 86.7%, and the OS rate with organ preservation was 62.2%. Distant metastasis control at 5 years was achieved in 85.4% of the patients. Distant metastasis was the most common cause of treatment failure; however, they reported that multiagent CCRT could improve the organ preservation rate and the outcome in the majority of appropriately selected patients with locoregionally advanced SCCHN. Bensadoun et al. [23] applied a more aggressive PF regimen for unresectable carcinomas of the oropharynx and hypopharynx in a phase III multicenter trial concurrently with twice-daily RT (two fractions of 1.2 Gy/day), 5 days per week. The PF regimen consisted of CDDP [100 mg/m^2/day: (days 1, 22 and 43)] and 5-day continuous infusion of 5-FU (750 mg/m^2/day: cycle 1; 430 mg/m^2/day: cycles 2 and 3). In their study, 163 evaluable patients were enrolled (82 patients treated with

Table 5 Toxicities

	TPF				$n = 48$		PFML				$n = 48$		Fisher's test
	Grade				All	Grade 3–4	Grade				All	Grade 3–4	P value
	I	II	III	IV	(%)	(%)	I	II	III	IV	(%)	(%)	(G3–4)
Neutropenia	0	0	9	7	33	33	0	2	7	0	19	15	0.031
Leukopenia	2	5	26	7	83	69	2	4	14	3	48	35	0.001
Thrombocytopenia	#	0	0	1	23	2	5	2	0	0	15	0	0.315
Anemia	4	1	2	0	15	4	2	3	2	0	15	4	1.00
Hypo albuminemia	0	0	0	0	0	0	0	0	1	0	2	2	0.315
ALT	#	0	1	1	27	4	8	0	1	0	19	2	0.558
AST	#	1	0	1	27	2	8	0	1	0	19	2	1.00.
Alkaline phosphatase	0	0	0	0	0	0	1	0	0	0	2	0	–
Bilirubin	1	0	0	0	2	0	0	0	0	0	0	0	–
Creatinine	2	0	0	0	4	0	2	3	1	0	13	2	0.315
GFR	0	1	0	0	2	0	0	1	0	0	2	0	–
Hypersensitivity	0	0	0	1	2	2	0	0	0	0	0	0	0.315
Nausea	1	0	16	0	35	33	5	3	9	0	35	19	0.104
Anorexia	0	0	1	0	2	2	0	0	0	0	0	0	0.315
Diarrhea	4	1	3	0	17	6	1	1	1	0	6	2	0.307
Fever	3	1	1	0	10	2	5	1	0	0	13	0	0.315
Infection	0	0	0	0	0	0	0	0	1	0	2	2	0.315
Infection with Grade 3 or 4 neutropenia	0	0	1	0	2	2	0	0	0	0	0	0	0.315
Mucositis	0	7	16	3	54	40	1	2	30	4	77	71	0.002
Dermatitis associated with radiation	0	4	17	2	48	40	1	2	23	5	65	58	0.067
Dysphagia	0	3	12	0	31	25	0	2	11	0	27	23	0.811
Pain	1	5	11	0	35	23	3	1	10	2	33	25	0.811
Deliria	0	0	0	0	0	0	0	0	1	0	2	2	0.315
Ileus	0	0	0	0	0	0	0	0	1	0	2	2	0.315
Ulcer, GI	0	1	0	0	2	0	0	0	0	0	0	0	–
Hemorrhage	0	0	1	0	2	2	0	0	0	0	0	0	0.315
Neuropathy-motor	0	0	0	0	0	0	0	1	0	0	2	0	–

RT alone and 81 with CCRT). There was no significant difference in Grade 3/4 mucositis (82.6%: CCRT group; 69.5%: RT alone group). However, there was a significant difference in Grade 3/4 neutropenia (33.3%: CCRT group; 2.4%: RT alone group; $P < 0.05$). At 24 months, OS and disease-free survival were significantly better in the group receiving CCRT with PF.

A meta-analysis of randomized clinical trials of NAC with TPF has shown that this TPF regimen significantly improves the survival of patients advanced SCCHN compared with the PF regimen [5]. Recent 2 randomized studies of NAC regarding the comparison between TPF and PF have shown that NAC with TPF improves the outcome of advanced, resectable and unresectable SCCHN with a reduction of more than 20% in the risk of disease progression or death compared with PF [7, 8]. Docetaxel represents a new class of cytotoxic agents having a specific antitumor mechanism in addition to the PF regimen.

From the results of phase I studies of the TPF regimen [11, 12], we compared NAC with TPF followed by definitive RT and CCRT with TPF in patients with locally advanced SCCHN. Both regimens were well tolerated and showed an almost similar pCR rate (87%: NAC group; 84%: CCRT group); however, the CCRT group showed a significantly better OS rate than the NAC group ($P = 0.04$) [14].

On the other hand, our previous studies have clarified that CCRT with PFML is safe and shows a high CR rate, resulting in good prognosis in patients with locally advanced SCCHN [15–17]. The organ preservation treatment approach using CCRT with PFML has shown high survival and larynx preservation rates with resectable stage III and IV SCC of the larynx and hypopharynx [15].

CCRT toxicity is a major concern, particularly with a potential chemotherapeutic regimen. Thirty-seven of 48 patients (77.1%) in the PFML group and 39 of 48 patients

(81.3%) in the TPF group received planned CCRT. For CCRT with PFML, the main toxicities were mucositis, leukocytopenia and neutropenia similar to previous studies [16, 17]. Severe mucositis was the most common AE in the PFML group and was more frequent than that in the TPF group. Early nutritional support by nasogastric tube feeding at 20–30 Gy after the first chemotherapy course and analgesic administration sustained the CCRT. Severe mucositis did not interrupt the planned treatment schedule in both groups. Leukocytopenia and neutropenia were common and more frequent toxicities in the TPF group than in the PFML group.

Both regimens showed high ORRs after CCRT completion (94%: PFML group; 98%: TPF group). The ORR, pCR rate and 3-year survival rate were almost identical to results of previous studies on CCRT with PFML [16, 17]. Regarding the CR rate, the TPF group showed a better pCR rate than the PFML group (90 vs. 77%), but the difference was not significant. There were also no significant differences in terms of the OS and RFS rates between the two groups in favor of the TPF group.

In conclusion, CCRT with TPF or PMFL was safe and tolerable. The most common and severe adverse events in the CCRT with multiagent chemotherapy were mucositis and hematological toxicities. Despite reservations, CCRT may achieve improved disease control. The overall response and CR rates were the same between the two types of chemotherapy in favor of CCRT with TPF in terms of the 3-year survival rate.

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The efficacy and safety of concurrent chemoradiotherapy for maxillary sinus squamous cell carcinoma patients

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Abstract

Objective: Combined treatment modality, e.g., definitive surgery followed by radiotherapy (RT) and definitive RT with concurrent chemotherapy, has been applied for advanced maxillary sinus squamous cell carcinoma (MSSCC) patients to obtain a better survival with organ preservation in Japan.

Methods: The outcome of 40 patients with MSSCC between 1991 and 2007 in our institute was analyzed retrospectively. There were 36 males and 4 females, the average age being 59.5 years (ranging from 34 to 81 years). The median follow-up time was 66.1 months. All the patients had received a combined treatment consisting of definitive surgery, RT, and intra-arterial or systemic chemotherapy. The chemotherapeutic regimen was different depending on the performance status and/or complications of the patients. Since 1998, concurrent chemoradiotherapy with cisplatin, 5-fluorouracil, methotrexate and leucovorin regimen (CCRT–PFML) instead of neo-adjuvant chemotherapy has been applied.

Results: The overall 5-year survival rate was 59.2%, the 5-year disease-specific survival rate was 71.7%, and the 5-year organ preservation survival rate was 42.4%. In the group receiving CCRT–PFML, the overall 5-year survival rate was 60.0%, the 5-year disease-specific survival rate was 76.0%, and the 5-year organ preservation survival rate was 60.3%.

Conclusion: CCRT–PFML for advanced MSSCC patients is feasible to preserve the organs without reducing the survival rate.

Keywords: Maxillary sinus carcinoma; Radiotherapy; Surgery; Chemotherapy; Chemoradiotherapy

1. Introduction

About 80% of malignant tumors in the maxillary sinus are histopathologically squamous cell carcinomas (SCCs) in Japan [1]. Furthermore, about 90% of the cases with SCC are in an advanced T stage at the first visit to hospital [1]. Patients with an early T stage have few symptoms, since the maxillary sinus is composed of bone structures. The definitive treatment modality for locoregionally advanced maxillary sinus squamous cell carcinoma (MSSCC) is radiotherapy (RT) and/or surgical resection similar to that for other head and neck squamous cell carcinomas (HNSCCs). Because of the anatomical features of the head and neck including the maxillary sinus, organ preservation is important to keep functions, e.g., phonation, deglutition and vision, and to minimize the aesthetic appearance changes. To preserve these functions, recent reports have described the efficacy of neo-adjuvant (induction) chemotherapy (NAC) followed by definitive RT and concurrent chemoradiotherapy (CCRT) for the advanced HNSCC patients [2–6]. According to the report of Sato et al. [7], the

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standard treatment method for advanced MSSCC in Japan has been a combination of surgery, RT and intra-arterial regional chemotherapy via the superficial temporal artery. The treatment modality for MSSCC has been modified by other clinicians [1,8,9]. From July 1991 to October 1997, patients with advanced MSSCC had been treated with NAC followed by RT, and since November 1997 till now, CCRT including cisplatin (CDDP), 5-fluorouracil (5-FU), methotrexate and leucovorin (CCRT–PFML) [6,10] has been mainly applied. For the patients with complications and/or the elderly, RT with weekly carboplatin (CBDCA) administration and UFT (CCRT–CU), one of oral 5-FU derivatives composing of tegafur and uracil, has been applied. Here we present the treatment efficacy of CCRT–PFML and the possibility of organ preservation for advanced MSSCC patients, in comparison with NAC and CCRT–CU.

2. Patients and methods

2.1. Eligibility criteria

Eligibility criteria included the followings: untreated stage III and IV patients with squamous cell carcinoma of the maxillary sinus; the disease that was measurable in at least one dimension; TNM disease according to the 2002 staging classification system of the Union International Contre le Cancer (UICC) without other active carcinomas, the staging evaluated by endoscope, computed tomography (CT) scan, magnetic resonance imaging (MRI) and ultrasonographic (US) findings of the neck; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1; life expectancy >3 months. Surgical resectable criteria excluded the patients with invasion to the brain, temporal fossa or apex of the orbital fossa.

2.2. Treatment schedule

Prior to the treatment, all the patients received maxillary sinus antrotomy for the pathological diagnosis. At the same time, catheter insertion into the superficial temporal artery of the affected side was performed. The catheter was fixed after confirming the tumor stained by indigocarmine injection.

From July 1991 to October 1997, patients had received neo-adjuvant chemotherapy (NAC) with a potential chemotherapeutic regimen (PFML) followed by RT, and since November 1997 till now, concurrent chemoradiotherapy with a potential regimen (CCRT–PFML) has been applied for the cases according to the following criteria; age between 20 and 75 years; sufficient bone marrow function (neutrophil count of >2000 cell/mm^3 and platelet count of >100,000 per mm^3); without significant abnormalities in the liver, heart, lungs, and kidneys (24 h creatinine clearance rate > 65 ml/(min 1.73m^2)); without active peptic ulcer diseases; without brain infarction and subarachnoid hemorrhage. The chemotherapy regimen consisted of a combination of four agents (PFML); CDDP (60 mg/m^2 for NAC and CCRT, day 4), 5-FU (800 mg/(m^2 day) for NAC and 600 mg/(m^2 day) for CCRT, days 1–5), methotrexate (MTX; 30 mg/m^2 for NAC and CCRT, day 1), and leucovorin (LV; 20 mg/m^2 for NAC and CCRT, days 1–5) [6,10]. CDDP was administrated intra-arterially and systemic 5-FU, MTX and LV were administrated intravenously. Two cycles of this regimen were given every 3 weeks for the NAC group and every 4 weeks during RT for the CCRT–PFML group. Other patients, not fulfilling the above-mentioned criteria, received RT with weekly carboplatin (CBDCA) and UFT (CCRT–CU). CBDCA was administrated intra-arterially once a week within 1 h prior RT, six to seven times during RT. The weekly CBDCA dose was determined by the area under the curve 1–1.25. The UFT was administrated in a daily oral dose of 300 mg as tegafur.

RT was given 5 days a week using a single daily fraction of 1.8 Gray (Gy) with 6 MV X-ray linear accelerators. The standard RT was given for the anterior and lateral fields, encompassing the primary tumor, and neck lymph nodes for node positive patients. After a total dose of about 40 Gy, all the patients were clinically re-evaluated with an endoscope, CT scan and/or MRI. The patients with a 50% or greater decrease (responders) in the product of two perpendicular diameters of primary and neck tumor continued RT and completed RT for a total dose of 66.6–70.2 Gy. For non-responders and recurrent patients after those therapies, definitive surgery was recommended for the resectable cases.

2.3. Response assessment

At 4–6 weeks after the end of RT or CCRT, the clinical response was assessed for each patient according to the combined findings of CT scanning, MRI, and US. A complete response (CR) was defined as a complete disappearance of all measurable lesions for at least 4 weeks. A partial response (PR) was defined as a 50% or greater decrease in the product of two perpendicular diameters of each and all measurable lesions for at least 4 weeks. The patients in whom the disease did not fulfill the criteria for PR were considered as having no change (NC) or a stable disease. The pathological responses to the RT or CCRT were confirmed by biopsy at the primary site in all the patients. In the patients with N1–3 lymph node disease, fine needle aspiration cytology of the neck lymph nodes was performed. The patients with less than CR of the primary and neck tumor (evaluated by histopathological examinations) were under consideration for a planned surgery 6–8 weeks after the end of the RT or CCRT.

The overall survival rate, the disease-specific survival rate and the organ preservation survival rate were calculated by the Kaplan–Meier method and were statistically analyzed by the Wilcoxon test.

Table 1
Patient characteristics.

	Overall (n = 40)	NAC (n = 16)	CCRT (n = 15)	RT (n = 9)
Age (years)				
Average	59.5	53.1	60.5	69.3
Range	34–81	34–75	41–75	47–81
Gender (n)				
Male	36	15	14	7
Female	4	1	1	2
T stage (n)				
1	0	0	0	0
2	1	1	0	0
3	11	3	5	3
4	28	12	10	6
N stage (n)				
0	36	13	15	8
1	1	1	0	0
2	3	2	0	1
3	0	0	0	0
Resectability (n)				
Resectable	32	15	10	7
Unresectable	8	1	5	2
Pathological differentiation (n)				
Poorly	12	4	4	4
Moderately	13	7	4	2
Well	15	5	7	3

2.4. Toxicity assessment

Toxicity was assessed during the treatment and 4 weeks after treatment using the 1998 National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0. The statistical analysis was calculated by Mann–Whitney's U test.

3. Results

3.1. Patient population

Between July 1991 and December 2007, 74 previously non-treated patients with malignant tumors in the paranasal sinuses had visited our institute, and 65 of the 74 patients had the primary site in the maxillary sinus. Of the 65 patients, 41 were the pathologically diagnosed as having squamous cell carcinoma. Forty patients were eligible (one patient was excluded because of distant metastases) for the present study. Thirty-six patients were male and four female, the average age being 59.5 years (range 34–81 years). Thirty-two patients were considered to be resectable and eight patients unresectable. Patients' characteristics were summarized in Table 1. The median follow-up time was 66.1 months (range 8–214 months). One patient died of an uncontrolled primary site tumor at 8 months after the treatment, one patient who showed CR died of alcoholic liver dysfunction at 8 months after the treatment, and one patient with NC after the treatment, died of pneumonia at 10 months after the treatment. Other 37 patients could be followed for more than 12 months.

3.2. Toxicity

The degrees of toxicity are listed in Table 2. Though the radiation related dysphagia (p = 0.002) and the radiation

Table 2
Toxicity.

NAC (n = 16) Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hematological					
Anemia	0	11 (68.8%)	3 (18.8%)	2 (12.4%)	0
Neutropenia	7 (43.8%)	5 (31.2%)	2 (12.5%)	2 (12.5%)	0
Thrombocytopenia	7 (43.8%)	9 (56.2%)	0	0	0
Non-hematological					
Diarrhea	11 (68.8%)	3 (18.6%)	2 (12.4%)	0	0
Fever	12 (75.0%)	2 (12.4%)	1 (6.3%)	1 (6.3%)	0
Hepatic					
AST	4 (25.0%)	11 (68.8%)	1 (6.2%)	0	0
ALT	3 (18.8%)	10 (62.4%)	3 (18.8%)	0	0
Nausea/vomiting	0	1 (6.2%)	2 (12.5%)	13 (81.3%)	0
Renal (creatinine)	15 (93.8%)	0	1 (6.2%)	0	0
Related to radiation					
Dermatitis	8 (50.0%)	5 (31.2%)	2 (12.6%)	1 (6.2%)	0
Dysphagia	16 (100%)	0	0	0	0
Mucositis	7 (43.8%)	4 (25.0%)	4 (25.0%)	1 (6.2%)	0
Pain	11 (68.8%)	3 (18.6%)	2 (12.6%)	0	0
CCRT (n = 15) Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hematological					

Table 2 (*Continued*)

Anemia	3 (20.0%)	5 (33.3%)	7 (46.7%)	0	0
Neutropenia	8 (53.3%)	2 (13.3%)	4 (26.7%)	1 (6.7%)	0
Thrombocytopenia	12 (80.0%)	2 (13.3%)	0	1 (6.7%)	0
Non-hematological					
Diarrhea	14 (93.3%)	1 (6.7%)	0	0	0
Fever	14 (93.3%)	1 (6.7%)	0	0	0
Hepatic					
AST	11 (73.3%)	4 (26.7%)	0	0	0
ALT	12 (80.0%)	3 (20.0%)	0	0	0
Nausea/vomiting	8 (53.3%)	2 (13.3%)	0	5 (33.4%)	0
Renal (creatinine)	15 (100%)	0	0	0	0
Related to radiation					
Dermatitis	6 (40.0%)	0	6 (40.0%)	3 (20.0%)	0
Dysphagia	8 (53.3%)	0	4 (26.7%)	3 (20.0%)	0
Mucositis	4 (26.7%)	3 (20.0%)	5 (33.3%)	3 (20.0%)	0
Pain	8 (53.3%)	0	4 (26.7%)	3 (20.0%)	0
RT ($n = 9$)					
Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hematological					
Anemia	0	6 (66.7%)	2 (22.2%)	1 (11.1%)	0
Neutropenia	4 (44.5%)	3 (33.3%)	1 (11.1%)	1 (11.1%)	0
Thrombocytopenia	3 (33.3%)	5 (55.6%)	1 (11.1%)	0	0
Non-hematological					
Diarrhea	8 (89.9%)	1 (11.1%)	0	0	0
Fever	9 (100%)	0	0	0	0
Hepatic					
AST	6 (66.7%)	2 (22.2%)	0	0	1 (11.1%)
ALT	6 (66.7%)	2 (22.2%)	0	1 (11.1%)	0
Nausea/vomiting	8 (89.9%)	0	1 (11.1%)	0	0
Renal (Creatinine)	5 (55.6%)	4 (44.4%)	0	0	0
Related to radiation					
Dermatitis	4 (44.5%)	1 (11.1%)	2 (22.2%)	2 (22.2%)	0
Dysphagia	6 (66.7%)	0	2 (22.2%)	1 (11.1%)	0
Mucositis	4 (44.4%)	0	5 (55.6%)	0	0
Pain	1 (11.1%)	1 (11.1%)	6 (66.7%)	1 (11.1%)	0

related pain ($p = 0.019$) were significantly severer in the CCRT–PFML group comparing to the NAC group, the toxicities were all tolerable and no fatal case was observed.

3.3. Treatment response

The response rate and recurrence rate of CR cases were summarized in Table 3. In all, 34 out of 40 patients (85.0%) showed pathological CR at the primary site, and 2 out of 4 patients (50%) with node positive patients showed cytological CR at the lymph nodes. The recurrence rate at the primary site was 29.4% (10 out of 34 CR patients) and that of lymph nodes in the neck was 0% (0 of 2 CR patients) in the all the cases. In the NAC group, the recurrence rate was 25.0% (3 of 12) at the primary site and 0% (0 of 1) at the lymph nodes, 21.4% (3 of 14) at the primary site in the CCRT–PFML group, and 50.0% (4 of 8) at the primary site and 0% (0 of 1) at the lymph nodes in the CCRT–CU group. Salvage dissection of the primary site was performed for 13 patients, i.e., 8 in the NAC group, 2 in the CCRT–PFML group and 3 in CCRT–CU group.

3.4. Survival

The overall 5-year survival rate was 59.2% in all the cases, 67.6% in the resectable cases and 25.0% in the unresectable cases ($p = 0.011$). The 5-year disease-specific survival rate was 71.7% in all the cases, 78.5% in the resectable group and 41.7% in the unresectable group ($p = 0.018$). The 5-year organ preservation survival rate was 42.4% in all the cases, 42.1% in the resectable group and 41.7% in the unresectable group (not significant; ns) (Fig. 1). In terms of the difference in the treatment method, the overall 5-year survival rate was 62.5% in the NAC group, 60.0% in the CCRT–PFML group and 53.3% in the CCRT–CU group (ns). The 5-year disease-specific survival rate was 73.3% in the NAC group, 76.0% in the CCRT–PFML group and 62.2% in the CCRT–CU group (ns). The 5-year organ

Table 3
Treatment response rate and recurrence rate of CR cases.

	Pathological CR	Pathological NC	Recurrence of CR
Primary (%)			
Overall ($n = 40$)	85.0	15.0	29.4 (10/34)
NAC ($n = 16$)	75.0	25.0	25.0 (3/12)
CCRT ($n = 15$)	93.3	6.7	21.4 (3/14)
RT ($n = 9$)	88.9	11.1	50.0 (4/8)
	Cytological CR	Cytological NC	Recurrence of CR
Lymph node (%)			
Overall ($n = 4$)	50.0	50.0	0 (0/2)
NAC ($n = 3$)	33.3	66.7	0 (0/1)
CCRT ($n = 0$)	N/A	N/A	N/A
RT ($n = 1$)	100	0	0 (0/1)

preservation survival rate was 35.2% in the NAC group (NAC vs. CCRT–CU; ns), 60.3% in the CCRT–PFML group (CCRT–PFML vs. NAC; $p = 0.020$) and 22.2% in the CCRT–CU group (CCRT–PFML vs. CCRT–CU; $p = 0.040$) (Fig. 2). Regarding the T stage, the overall 5-year survival rate was 100% in T2 patients, 69.0% in T3 patients and 53.6% in T4 patients (ns). The 5-year disease-specific survival rate was 100% in T2 patients, 76.0% in T3 patients and 68.2% in T4 patients (ns). The 5-year organ preservation survival rate was 0% in T2 patients, 50.9% in T3 patients and 41.1% in T4 patients (ns) (Fig. 3).

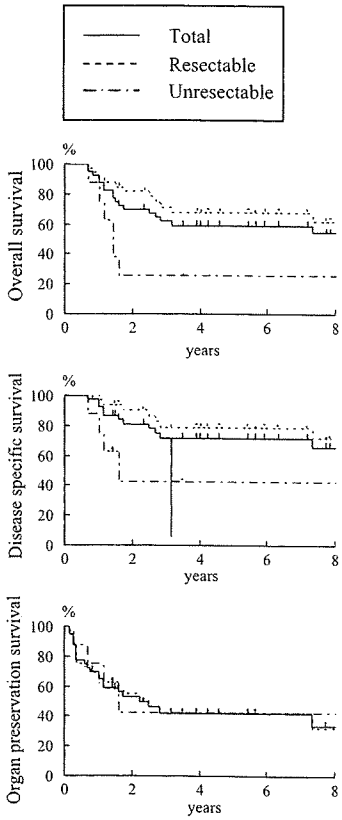

Fig. 1. The overall 5-year survival rate, the 5-year disease-specific survival rate and the 5-year organ preservation survival rate were shown, in terms of the resectability.

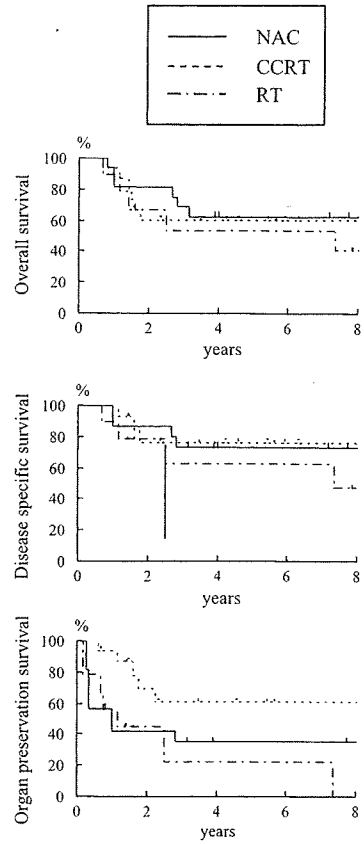

Fig. 2. The overall 5-year survival rate, the 5-year disease-specific survival rate and the 5-year organ preservation survival rate were shown, in terms of the treatment modality.

4. Discussion

The maxillary sinus carcinomas (MSCs) are not common, i.e., the incidence rate 0.2–0.5% of all carcinomas, 3% of all head and neck carcinomas and 80% of all paranasal sinus carcinomas in the United States and European countries [11]. The incidence of MSC in Asia is higher than that in Western countries. However, MSC has been decreasing in Japan. Since July 1991 to December 2007, the incidence of MSC had been 6.5% of all cases of head and neck carcinoma and 87.8% of all cases of paranasal sinus carcinoma at our institute. These incident rates were almost similar to those of other institutes in Japan. The maxillary sinus consists of facial bones, and the symptoms of MSC are commonly associated with the destruction of the bony walls surrounding the maxillary sinus. Most of the MSC patients visit hospital with cheek pain, cheek swelling, nasal obstruction and nasal bleeding induced by advanced tumors. MSC patients in the early stage do not have such typical symptoms. The overall 5-year survival rate of MSC is 34–59% [12–14]. The survival rate depends not only on the

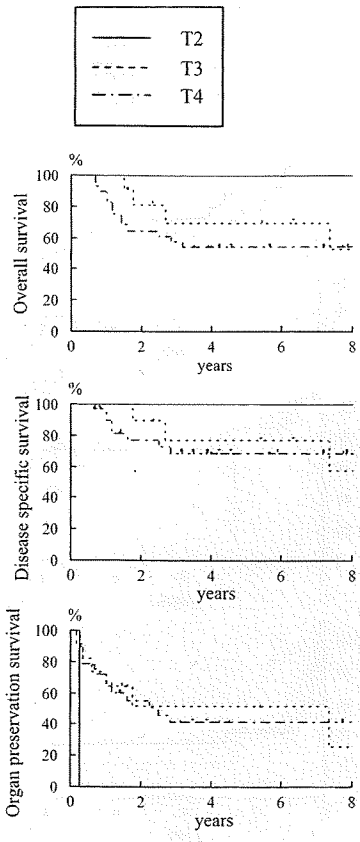

Fig. 3. The overall 5-year survival rate, the 5-year disease-specific survival rate and the 5-year organ preservation survival rate were shown, in terms of the T stage.

T stage, but also on the histological type and the presence of lymph node metastasis [12–16]. Referring to the previous reports from Western countries, the incidence of each pathological type is as follows; squamous cell carcinoma (40–60%), adenoid cystic carcinoma (20–25%), undifferentiated carcinoma (4–17%), and adenocarcinoma (4–5%) [12,14,15]. On the other hand, most of the pathological diagnoce of MSC is squamous cell carcinoma (SCC) in Japan, i.e., 84.6% at our institute. Regarding MSSCC, the overall 5-year survival rate varies from 45.2 to 77% [1,17–19]. The reason of the good outcome might be related to the patients population in the early stage, e.g., 12.0% of T2 and 57.3% of T3 cases [1].

Because of the anatomical features of the head and neck including the maxillary sinus, organ preservation is important to keep the function, e.g., phonation, deglutition and vision, and also to minimize the aesthetic appearance changes. The treatment modality of resectable head and neck SCC (HNSCC) has apparently changed over the past century [20]. Surgery followed by RT is the most accepted treatment for the resectable cases. However, the cure rate has not exceeded 30% because of the high rate of locoregional failure (60%) or distant metastasis (20%) [21]. The treatment modality including CDDP-based neo-adjuvant (induction) chemotherapy (NAC) has been used since the 1970s and has shown the benefit of organ preservation and reduction of the distant metastasis rate. On the other hand there is a controversy on the survival elongation [22–25]. 5-FU is frequently administered as the basic agent of chemotherapy regimens for HNSCC since it has a synergistic interaction with many anti-neoplastic agents. NAC including CDDP and 5-FU (PF regimen) has been the standard therapy for locoregionally advanced and recurrent HNSCCs [22]. In randomized trials of NAC, the response rate of PF regimen ranges from 60 to 80% with the clinical CR rate being 20–30% [26]. To preserve organs and function, recent papers have described the efficacy of NAC followed by definitive RT alone or followed by CCRT with CDDP or CBDCA for advanced HNSCC patients [2–6,27]. We had modified the PF regimen, i.e., the combination with MTX and LV in addition to CDDP administration during the continuous infusion of 5-FU (PFML) [6,10], because the CDDP administration after starting the 5-FU infusion showed a higher CR rate than the conventional PF regimen. Furthermore, the combination of MTX and 5-FU showed synergistic cytotoxic effects and the co-administration of LV indicated the enhancement of 5-FU cytotoxicity [28–31]. Advanced HNSCC patients without severe complications had been treated by NAC with PFML regimen followed by RT form July 1991 to October 1997, and CCRT using dose modified PFML regimen (CCRT–PFML) has been applied for advanced HNSCC patients since November 1997 till now.

The maxillary sinus is surrounded by the bony structure which is a structural barrier to local invasion, regional lymph node metastasis and distant metastasis of tumors. Based on the report of Sato et al. [7], the standard treatment method for MSSCC in Japan has been the combination of surgery, RT and intra-arterial regional chemotherapy via the superficial temporal artery. The treatment efficacy of intra-arterial chemotherapy for MSC is according to reports [7,17,32–36]. Because of the expectation for the effectiveness of chemotherapeutic agent, we have been applying the intra-arterial chemotherapy of CDDP for advanced MSSCC patients in addition to the systemic administration of 5-FU, MTX and LV to eradicate micro-disseminated tumor cells. For the elderly and/or compromised advanced HNSCC patients, CCRT with CBDCA plus UFT (CCRT–CU) has been applied with good results [37]. As a sensitizer to radiation, CBDCA has been administred intra-arterially to enhance the local efficiency and UFT is administrated orally for the systemic efficiency.

The 5-year disease-specific survival rate was 71.7% in all the cases, 73.3% in the NAC group, 76.0% in the CCRT–PFML group and 62.2% in the CCRT–CU group in the present study and these results are comparable with other reports [1,17,18,38]. The survival rate was better in the resectable cases than in the unresectable cases as in other reports, and the early T stage cases showed a better survival rate than advanced cases. The 5-year organ preservation survival rate was 42.4% and this rate is slightly better than