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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

(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

RANDOMIZATION	TPF	Docetaxel	50 mg/m2 iv day 1
		Cisplatin	60 mg/m2 iv day 4
		5-fluorouracil	600 mg/m2/day civ days 1-5
			every 4 weeks x 2 courses
		Radiation	2 Gy/day x 5 days/w x 6 weeks
	PFML	Cisplatin	60 mg/m2 iv day 4
		5-fluorouracil	600 mg/m2/day civ days 1-5
		Methotrexate	30 mg/m2 iv day 1
		Leucovorin	20 mg/m2 iv days 1-5
			every 4 weeks x 2 courses
		Radiation	2 Gy/day x 5 days/w x 6 weeks

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

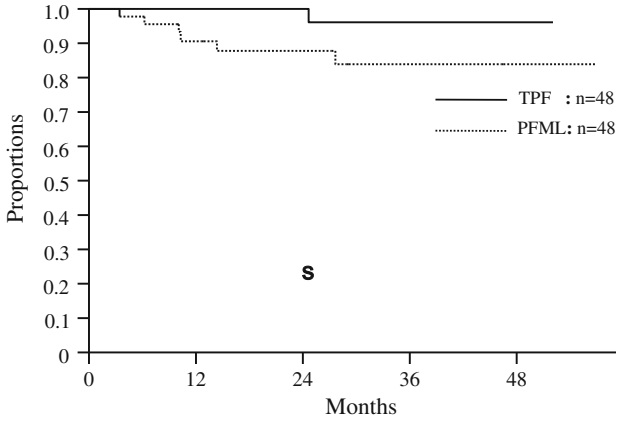

Fig. 1 Kaplan–Meier overall survival curves. The 3-year overall survival rates were 83.8% in the PFML group and 95.8% in the TPF group

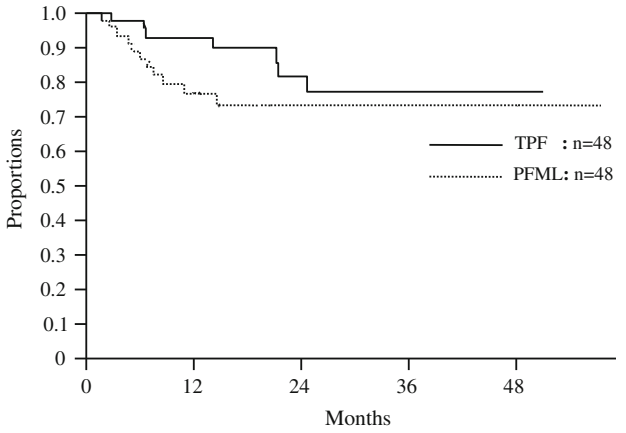

Fig. 2 Kaplan–Meier relapse-free survival curves. The 3-year relapse-free survival rates were 73.3% in the PFML group and 77.4% in the TPF group

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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