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ORIGINAL ARTICLE

Analysis of efficacy and toxicity of chemotherapy with cisplatin, 5-fluorouracil, methotrexate and leucovorin (PFML) and radiotherapy in the treatment of locally advanced squamous cell carcinoma of the head and neck

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Abstract
Purpose The aim of this study was to evaluate the efficacy and toxicity of concurrent chemoradiotherapy using cisplatin (CDDP), 5-fluorouracil (5-FU), methotrexate (MTX) and leucovorin (LV) (PFML) in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).
Methods Seventy-seven patients with previously untreated stages III–IV SCCHN were included in this trial. Patients received two cycles of chemotherapy repeated every 4 weeks. The chemotherapy regimen consisted CDDP (60 mg/m^2, day 4), 5-FU (600 mg/m^2 given over 24 h for 5 days, days 1–5), MTX (30 mg/m^2, day 1) and LV (20 mg/m^2, days 1–5). Radiation was targeted to begin on the starting day of chemotherapy, day 1. The total radiation dose to the primary site and neck lymph nodes was 70.0 Gy. When grade ≥3 toxicities were observed frequently, radiotherapy and/or chemotherapy were delayed or reduced.
Results The main toxicities were mucositis (grade ≥3, 39%), leukocytopenia (grade ≥3, 34%) and neutropenia (grade ≥3, 30%). The overall clinical response rate and the pathological complete response (CR) were 94% (72/77) and 71% (55/77). The primary site CR and neck lymph node CR were 79% (61/77) and 85% (44/52), and 3-year survival rate was 73%.
Conclusions This concurrent chemoradiotherapy with PFML was safe and well tolerated. The high CR rate justifies further evaluation of this chemoradiotherapy modality in locally advanced SCCHN patients.

Keywords Chemoradiotherapy · Cisplatin · 5-Fluorouracil · Methotrexate · Leucovorin · Squamous cell carcinoma of the head and neck (SCCHN)

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Introduction

In the majority of patients with squamous cell carcinoma of the head and neck (SCCHN), the disease is locally advanced at presentation, and 5-year survival rates remain below 30% [1–6]. During the past 10 years, combined modality approaches have been developed in an effort to enhance locoregional disease control, reduce distant metastatic spread, and improve survival in patients with locally advanced or inoperable SCCHN. Multidisciplinary treatment including chemotherapy that has antitumor activity when used by itself, or radiosensitizing effects when combined with radiotherapy, has been employed to improve outcome of such patients.

Randomized trials have demonstrated that neoadjuvant treatment with cisplatin (CDDP) plus 5-fluorouracil (5-FU) (PF) obviates the need for surgery in

patients with resectable laryngeal and hypopharyngeal cancer, without affecting survival [7, 8]. PF was also shown to improve survival and disease-free survival in patients with unresectable SCCHN when administered with definitive radiotherapy [9]. Regimens including PF are currently considered standard chemotherapy for patients with locally advanced SCCHN. Overall response rate with PF in previously untreated, advanced SCCHN is approximately 80%, with complete response (CR) rates of 20–45% [10, 11]. CR in chemotherapy, particularly pathological CR, is a positive prognostic factor in SCCHN.

A recent systematic review using meta-analysis has revealed that chemotherapy given concurrently to radiotherapy shows a significant benefit for survival rate of patients with SCCHN, when compared with radiotherapy alone, and was superior to induction chemotherapy with PF [12]. Combination of PF yielded higher response rates than single agents such as methotrexate (MTX) [12, 13].

In this study, we report the results of phase II trial of aggressive concurrent chemoradiotherapy with CDDP, 5-FU, MTX and leucovorin (LV) (PFML) in patients with locally advanced SCCHN. Before this trial, we had carried out initial trial of concurrent chemoradiotherapy with PFML for patients with locally advanced SCCHN [14]. The main endpoints of this study were to evaluate the toxicity of this concurrent chemoradiotherapy and to obtain preliminary assessment of the efficacy of this regimen in patients with advanced and untreated SCCHN.

Patient and methods

Patient population

Patients were selected if they had histologically or cytologically confirmed SCCHN, at least one unidimensionally measurable lesion, and stage III or IV disease without evidence of distant metastases. Patients with primary sites in the nasopharynx, oropharynx, hypopharynx, larynx, oral cavity or paranasal sinus were eligible. Patients who had received previous chemotherapy, radiotherapy or surgery were excluded. Patients were ineligible if they had another cancer.

Patients were required to be from 20 to 75 years of age and have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, life expectancy of more than 3 months, WBC count of $\geq$4,000 cells/μL, absolute neutrophil count (ANC) of $\geq$2,000 cells/μL, platelet count of $\geq$100,000 μL^{-1}, hemoglobin level of $\geq$9.5 g/dL, AST, ALT and alkaline phosphatase level below 2.5 times the upper limit of normal (ULN), total bilirubin and creatinine levels below 1.5 times ULN, BUN level below ULN and 24-h creatinine clearance rate of more than 60 mL/min. Patients with significant cardiac arrhythmia or heart failure were ineligible. All patients provided written informed consent prior to enrollment into the study, and this study had been approved by the institution's IRB.

Treatment schedule

This study was phase II trial of aggressive concurrent chemoradiotherapy with PFML in patients with locally advanced SCCHN. Before this trial, we had carried out initial trial of concurrent chemoradiotherapy with PFML for patients with locally advanced SCCHN [14]. The chemotherapy regimen consisted of a combination of four drugs: cisplatin (60 mg/m^2, day 4), 5-FU (600 mg/m^2 given over 24 h for 5 days, days 1–5), MTX (30 mg/m^2, day 1) and LV (20 mg/m^2, days 1–5). Two cycles of this regimen were given every 4 weeks during radiotherapy. Administration schedule are shown in Fig. 1. When grade $\geq$3 toxicities were observed frequently and continued over 5 days, chemotherapy was delayed within 14 days.

Radiotherapy (2.0 Gy/fraction day) administered 5 days per week was delivered to the primary tumor site and neck, and was targeted to begin on the starting day of chemotherapy, day 1. The total dose to the primary tumor site and neck lymph nodes was 70.0 Gy. Every effort was made to continue radiation on schedule. Subcutaneous G-CSF 100 μg/day was injected if the neutrophil count was less than 1,000 cells/μL after chemotherapy. When grade $\geq$3 toxicities were observed frequently and continued over 5 days, radiotherapy was

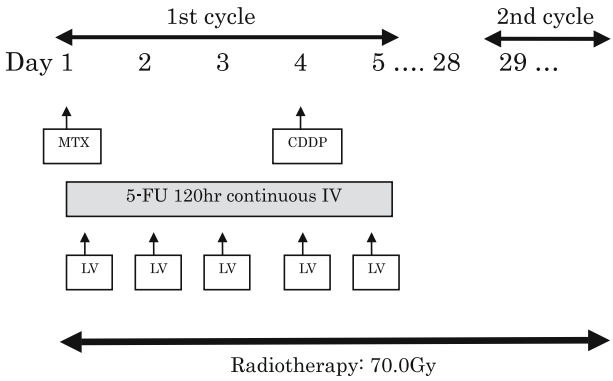

Fig. 1 Administration schedule of concurrent chemoradiotherapy with cisplatin, 5-FU, MTX, and LV in patients with locally advanced SCCHN. *IV* intravenous infusion

delayed for about 3 days. The toxicities were continued more than 10 days, radiotherapy was reduced 4.0 Gy.

Re-treatment on day 29 required ANC of ≥2,000 cells/μL, a platelet count of ≥100,000 μL^{-1}, hemoglobin level of ≥9.5 g/dL, AST, ALT and alkaline phosphatase level below 2.5 times the upper limit of normal (ULN), 24-h creatinine clearance rate of more than 50 mL/min and resolution of all other non-hematological toxicities (except alopecia, musculoskeletal pain and fatigue) to baseline or less than grade 1. If there were some toxicities as above, cycle 2 chemotherapy was delayed, and if the delay was beyond 14 days, the patient was removed from the study.

Patients were monitored for toxicity (medical interview, physical examination and complete blood cell counts) during treatment. Blood and urine chemistries were performed two or three times a week.

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 effects such as myelosuppression, mucositis, fever (>38.0 °C) and other disorders was required prior to initiating the second treatment cycle.

Clinical response and further treatment

Clinical response was defined for each patient according to the combined findings of CT, MRI and ultrasonic examination at the day after 3 weeks from the end of the chemoradiation therapy. The criteria used to evaluate complete response (CR), partial response (PR), no change (NC) and progressive disease (PD) were based on the standard definitions established by the WHO [15]. Clinical responses of this chemoradiation therapy were confirmed by biopsies of the primary site in all cases. In the case of N1–3, fine needle aspiration cytology of the neck lymph nodes was performed. Responses in the primary site and the regional nodes were scored separately and the overall response based on the worst of the two responses. Surgery of the primary tumor site was recommended for operable patients with resectable disease who failed to achieve CR after the end of chemoradiation therapy. Surgery was carried out routinely 4–6 weeks after the end of chemoradiation therapy. Planned neck dissection was not performed.

We considered the criteria of unresectable patients with SCCHN as follows: (1) with invasion to the prevertebral fascia and muscle; (2) with common or internal carotid artery invasion that was concluded to be unable to remove as a result of the artery occlusion test.

With these criteria, we considered that, excluding the patients with nasopharyngeal cancer, 17 patients (four oropharnx, seven hypopharynx, five Larynx and one oral cavity) were considered resectable at study entry.

Study design

This study was a prospective study. The main end points of this study were the toxicity of this concurrent chemoradiotherapy and preliminary assessment of the efficacy of this regimen in patients with advanced and untreated SCCHN.

Follow-up

Once treatment ended, patients were evaluated at 2 weeks, then every month from the first 1 year, every 2 months from 1 through 3 years, every 3 months from 3 through 5 years, and annually thereafter.

Result

Characteristics of the patients

From January 2000 to March 2006, 77 eligible patients who visited Department of Otolaryngology, Yokohama City University Medical Center, Yokohama, Japan, were identified. Table 1 outlines the characteristics of the patients. Sixteen patients were male and three were female, average age was 53.2 years (range, 32–74 years). Performance status (ECOG) was 0 in 50 patients and 1 in 27 patients. Primary disease sites were nasopharynx ($n = 14$), oropharynx ($n = 15$), hypopharynx ($n = 22$), larynx ($n = 20$) and oral cavity ($n = 6$). Forty patients had stage III disease and the remaining 37 patients were stage IV. Forty patients (52%) had N2 ($n = 25$) or N3 ($n = 15$) status before treatment and 15 patients had N0 status.

Treatment

When grade ≥3 toxicities were observed frequently, radiotherapy and/or chemotherapy were delayed or reduced. In radiotherapy, the mean dose delivered to the primary tumor was 69.4 Gy (rage, 66–70 Gy). The average numbers of days of administration were 51 days (range, 47–53 days). In chemotherapy, all patients received two cycles of chemotherapy. Sixty-nine patients received without delay, and eight received with 7 days delay.

Table 1 Baseline patient characteristics

Patient characteristic	No. of patients (n = 77)
Sex	
Male	62
Female	15
Age (years)	
Average (range)	53.2 (32–74)
Performance status	
0	50
1	27
Primary site	
Nasopharynx	14
Oropharynx	15
Hypopharynx	22
Larynx	20
Oral Cavity	6
T-stage	
T1	6
T2	17
T3	32
T4	22
N-stage	
N0	15
N1	22
N2	25
N3	15
Stage	
III	40
IV	37

Toxicity

Acute and late toxicities are listed in Table 2. Mucositis was the most common adverse effect observed and grade ≥3 mucositis occurred in 39% (30/77). Leukocytopenia and neutropenia were also observed frequently, and grade ≥3 leukocytopenia and neutropenia occurred in 34% (26/77) and 30% (23/77), respectively.

Table 2 Acute and late toxicities

	No. of patients (n = 77)	
Toxicity grade	3	4
Acute toxicities		
Leukocytopenia	10	16
Neutropenia	8	15
Anemia	6	0
Thrombocytopenia	4	0
Elevated AST, ALT level	5	0
Elevated creatinine level	3	0
Mucositis	30	0
Late toxicities		
Xerostomia	10	0
Subcutaneous	2	0
Bone	3	0
Skin	2	0

The patients with grade ≥3 mucositis needed nutrition supports. Thirteen patients needed naso-gastic tube feeding, ten gastrostomy tube feeding and nine total parenteral nutrition.

Outcome

Three weeks following completion of the chemoradiotherapy, all patients underwent biopsies of the primary tumor and/or fine needle aspiration cytology with ultrasound technique of neck lesions to determine the pathological response. As can be seen in Table 3, the overall clinical response rate and the pathological CR were 94% (72/77) and 71% (55/77), respectively. The primary site CR and metastatic lymph node CR were 79% (61/77) and 85% (44/52), respectively.

In patients with carcinoma in nasopharynx, CR, PR and NC were 79% (11/14), 21% (3/14) and 0%, respectively. In oropharynx, each rate was 73% (11/15), 20% (3/15) and 7% (1/15). In hypopharynx, each rate was 68% (15/22), 23% (5/22) and 9% (2/22). In larynx, each rate was 70% (14/20), 25% (5/20) and 5% (1/20). In oral cavity, each rate was 66% (4/6), 17% (1/6) and 17% (1/6).

There was no significant difference between each organ.

After the chemoradiotherapy, there were 17 PR patients and 5 NC patients. Thirteen patients received operation after chemoradiotherapy. Nine unresectable patients could not received operation: five patients with invasion to the prevertebral fascia and muscle, and four patients with common or internal carotid artery invasion that was concluded to be unable to remove as a result of the artery occlusion test.

The median follow-up of surviving patients was 34.9 months (range, 5–67). In Fig. 2, Kaplan–Meier estimate of cause-specific survival rate, and 3-year survival rate was 73%.

Table 3 Clinical response at primary site and metastatic lymph nodes

	No. of patients (n = 77)	
	Response: CR55, PR17, NC5	
	Site P	Site N
CR	61	44
PR	14	14
NC	2	4
PD	0	0
NE		15

P primary site; *N* metastatic lymph node; *NE* not evaluable because N0 at baseline

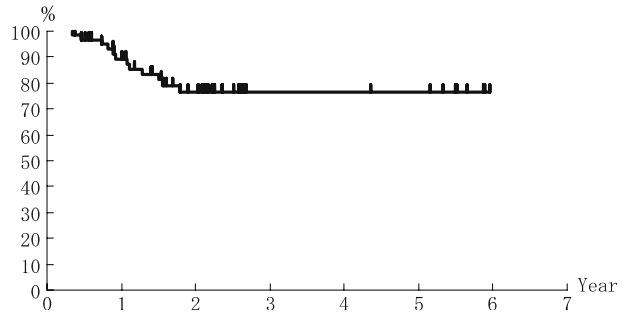

Fig. 2 Kaplan–Meier estimate of cause-specific survival rate. Five-year survival rate was 73%

Discussion

Chemotherapy and radiotherapy have been demonstrated to be highly effective in increasing survival in patients with unresectable disease in multiple studies. Concurrent chemoradiotherapy and induction chemotherapy have been established as an appropriate standard of care for many patients with locally advanced SCCHN.

Many studies have explored the PF chemotherapy followed by radiation in SCCHN. The most comparable phase III trial of PF chemotherapy followed by radiation was the European Organization for Research and Treatment of Cancer (EORTC) Hypopharynx Trial [2]. In the EORTC trial, patients were treated in chemotherapy with CDDP 100 mg/m^2 on day 1 and 5-FU 1,000 mg/m^2 day on days 1–5 every 4 weeks for three cycles, and afterwards, they were treated by radiation (70 Gy). In this trial, 51% had a clinical CR and they showed that PF chemotherapy followed by radiation was effective in increasing overall survival in unresectable disease, compared with radiotherapy alone. Using PF, Taylor et al. [16] showed comparison of concurrent chemoradiotherapy and chemotherapy followed by radiation for toxicity and efficacy in patients with SCCHN. This was a randomized trial between CDDP 60 mg/m^2 on day 1 plus 5-FU 800 mg/m^2 on days 1–5 plus radiation 2 Gy on days 1–5, repeated every other week for seven cycles, versus CDDP 100 mg/m^2 on day 1 plus 5-FU 1.0 g/m^2 on days 1–5, repeated every 3 weeks for three cycles, followed by 70 Gy of radiation in 7–8 weeks. After all treatment, CR was not different between the two groups (52% in concurrent chemoradiotherapy and 50% in chemotherapy followed by radiation); however, in overall response rates, concurrent chemoradiotherapy was better than chemotherapy followed by radiation ($p = 0.003$) (93% in concurrent chemoradiotherapy and 78% in chemotherapy followed by radiation), and fewer patients with no change or progression after concurrent treatment. Severe and worse toxic events were similar between the treatment programs. Concurrent chemoradiotherapy with PF offered improved disease control, predominantly of regional disease, better than chemotherapy followed by radiation.

The combination of MTX and 5-FU is an attempt to overcome the development of resistance of tumor cells to 5-FU. MTX followed by 5-FU produces a synergistic cytotoxic effect in vitro [17–19]. MTX inhibits purine synthesis and leads to intracellular accumulation of 5-phosphoribosyl-1-pyrophosphate (PRPP). After MTX exposure, there was an increase in intracellular PRPP pools, and subsequent incorporation of MTX into RNA [17, 18]. Finally, the addition to cell cultures of hypoxanthine, which utilizes PRPP, prevents the intracellular accumulation of ribonucleotides of 5-FU [19].

Another strategy to improve the effectiveness of chemotherapy including 5-FU is based upon the ability of LV to modulate cytotoxic effects of 5-FU. The laboratory rationale for the enhanced antitumor activity when LV is combined with 5-FU is stabilizing the 5-fluoro-2′-deoxyuridine-5′-monophosphate (FdUMP)–thymidylate synthase complex, thus increasing the block in the DNA synthetic pathway as a result of increasing the intracellular levels of reduced folates in the tumor [20]. LV concentration greater than 1 μmol/L was sufficient to produce enhancement of 5-FU cytotoxicity [21].

In the present study, mucositis was the most common adverse effect observed and grade ≥3 mucositis occurred in 39%. Gilles et al. showed the incidence of grade ≥3 mucositis in the concurrent chemoradiotherapy with PF was 65% and higher than in the radiotherapy-only (34%) [22]. Incidence of mucositis was not so different between concurrent chemoradiotherapy with PFML and PF. Leukocytopenia and neutropenia were also observed frequently, and grade ≥3 leukocytopenia and neutropenia occurred in 34% and 30%. Gilles et al. [22] also showed the incidence of grade ≥3 leukocytopenia and neutropenia in the concurrent chemoradiotherapy with PF was 42 and 39% and higher than in the radiotherapy-only (13 and 11%) [22]. There is no significant difference in hematological toxicity between concurrent chemoradiotherapy with PF and PFML. This study suggests that the toxicity of the concurrent chemoradiotherapy with PFML compares favorably with concurrent chemoradiotherapy with PF chemotherapy.

This concurrent chemoradiotherapy with PFML has major antitumor activity with manageable toxicity as

treatment in SCCHN patients. The high CR rate justifies further evaluation of this chemoradiotherapy combination. Based on high response rate shown in this study, we are conducting a randomized comparison of concurrent chemotherapy with PFML versus concurrent chemoradiotherapy with docetaxel, CDDP and 5-FU (TPF) [23–25].

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