Table 5 Successful salvage rate by T classification

T classification (no. of patients)	No. of patients (%)		
	Local recurrences/ residuals	Salvage surgeries	Successfully salvaged
T1 (18)	1	1 (100)	1 (100)
T2 (69)	10	5 (50)	3 (30)
T3 (38)	9	3 (33)	3 (33)
T4 (44)	15	2 (13)	1 (7)
Total (169)	35	11 (31)	8 (23)

Table 6 Successful salvage rate by subsite

Subsite (no. of patients)	No. of patients (%)		
	Local recurrences/ residuals	Salvage surgeries	Successfully salvaged
Lateral (105)	21	5 (24)	4 (19)
Anterior (45)	8	3 (38)	3 (38)
Superior (8)	2	1 (50)	0 (0)
Posterior (12)	4	2 (50)	1 (25)
Total (170)	35	11 (31)	8 (23)

Table 7 Swallowing function and larynx preservation in patients with local recurrence or residual disease after salvage surgery ($n = 11$)

Variable	No. of patients (%)	
	Preoperative	Postoperative
Nutrition		
Oral feeding	9 (82)	6 (55)
Oral and tube feeding	2 (18)	3 (27)
Tube feeding	0 (0)	2 (18)
Larynx preservation		
Yes	–	8 (73)
No	–	3 (27)

function disorders and required tube-feeding support after CRT. In contrast, in the patients undergoing salvage surgery, ages ranged from 42 to 75 years (median, 54 years), the rate of T4a disease was 18, and 18 % of patients required tube-feeding support after CRT. However, the presence of an advanced tumor is a high-risk factor for local failure and, moreover, the general condition after CRT in such cases is generally poor. Laryngeal cancer, by contrast, offers a greater opportunity for salvage surgery for local recurrence. One hundred and twenty-nine patients developed local recurrence in the RTOG 91-11 laryngeal cancer trial, and the disease was found to be resectable in all cases [12]. Consequently, there might be only a limited

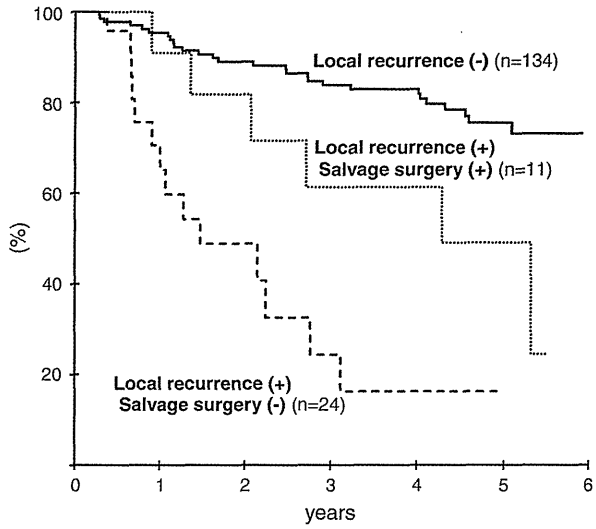

Fig. 3 Overall survival in 11 patients who underwent salvage surgery for local recurrence, 24 patients who did not undergo salvage surgery for local recurrence, and 134 patients who had no local recurrence

number of cases suitable for salvage surgery among patients who initially received CRT for advanced OPC and subsequently developed local recurrence.

Another point of controversy is that patients undergoing salvage surgery for local failure cannot always achieve long-term survival. In our study, 8 patients developed a second recurrence, including 3 cases of local recurrence, 3 of neck disease, and 5 of distant metastasis. Similarly, Zafereo et al. [11] reported that 26 of 39 patients (66.7 %) developed a second recurrence after salvage surgery. It has been regarded that patient age, disease-free interval, T and N classification of recurrent tumors, and surgical margin status influence survival and recurrence rate after salvage surgery for recurrent OPC [11, 13, 14]. However, at the moment, the fact remains that any salvage therapy is less effective than surgery. It is hoped that a novel adjuvant therapy after salvage surgery, such as molecular targeted drug therapy, will be developed in the future.

In this study, 10 patients (91 %) underwent microvascular free flap reconstruction for salvage surgery, with 5 patients (50 %) requiring tube-feeding support after surgery and the larynx preservation rate was 73 %. On the other hand, of the 40 patients who underwent reconstruction surgery with preoperative or postoperative irradiation as an initial treatment, 12 patients (31 %) required tube-feeding support after surgery and the larynx preservation rate was 78 %. Zafereo et al. [11] similarly reported that only 9 (22 %) patients required tube-feeding before salvage surgery, whereas 26 (64 %) required tube-feeding support after surgery. With regard to initial therapy for advanced OPC, it has been reported that patients treated with surgery show a statistically higher frequency of

swallowing disorders than those treated with CRT [15]. However, these results suggest that salvage surgery after CRT would worsen swallowing function in the patients in comparison with initial open surgery.

Chemoradiotherapy is more advantageous in organ and function preservation than definitive surgery; however, survival rates for patients treated with CRT are not always superior to those treated by surgery. Furthermore, it is difficult to salvage local failures, as already described. We have to make an effort to detect persistent tumor or recurrence as early as possible; this should lead to a higher salvage rate. In recent years, clinical trials of less-intensive therapy for patients with HPV-positive OPC have been undertaken by some groups. Considering the difficulty of salvage surgery, the initial treatment method for OPC should be decided carefully and the limitations of salvage surgery should be fully considered.

In conclusion, salvage surgery for OPC was indicated in a limited number of patients with local failure, and the survival rate of these patients was not so high as expected. In addition, swallowing function was worse in patients undergoing salvage surgery after CRT than in those undergoing initial open surgery. However, it is a fact that salvage surgery is the only curative treatment for the patients with recurrence after CRT in most cases. These results should be given adequate consideration when the initial treatment method for OPC is decided.

Conflict of interest No conflict of interest.

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Phase II Feasibility Trial of Adjuvant Chemoradiotherapy with 3-weekly Cisplatin for Japanese Patients with Post-operative High-risk Squamous Cell Carcinoma of the Head and Neck

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Objective: The current standard of care for post-operative high-risk squamous cell carcinoma of the head and neck is concurrent chemoradiotherapy with a 3-weekly cycle of cisplatin (3W-CDDP/RT). In previous pivotal trials, the complete delivery rate of three cycles of cisplatin and radiation therapy was only ~60%. Here, we evaluated the feasibility and safety of 3W-CDDP/RT in a Japanese population.

Methods: The study enrolled post-operative high-risk squamous cell carcinoma of the head and neck patients. High-risk factors were a microscopically incomplete resection, extracapsular extension and two or more lymph node metastases. Subjects received three cycles of cisplatin at a dose of 100 mg/m^2 concomitant with radiation therapy (66 Gy/33 Fr).

Results: From August 2006 to May 2009, 25 eligible subjects were accrued, including 13 males, with a median age of 59 years, Eastern Cooperative Oncology Group performance status 0/1 (18/7), Stage III/IVA/IVB/recurrent (1/18/1/5) and oral cavity/oropharynx/hypopharynx/larynx (17/4/3/1). Protocol completion rate was 80%. The lower limit of the one-sided 90% confidence interval was 66%, which met the predefined statistical criteria. Grade 3/4 acute and late toxicities were almost identical to those in previous pivotal trials. No treatment-related deaths were observed. With a median follow-up of 39 months, 14 have had progression and 10 have died. Estimated 3-year locoregional control rate, relapse-free survival and overall survival were 74, 43 and 60%, respectively. On univariate analysis, oral cavity cancer and a cumulative cisplatin dose below 240 mg/m^2 appeared to be poor prognostic factors.

Conclusions: This is the first Phase II feasibility trial of adjuvant chemoradiotherapy with 3-weekly cisplatin for post-operative high-risk squamous cell carcinoma of the head and neck in a Japanese population. This treatment was feasible and the safety profile was identical to those in pivotal Phase III trials.

Key words: head and neck cancer – post-operative high risk patients – adjuvant chemoradiotherapy – cisplatin

INTRODUCTION

The current standard of care for post-operative high-risk squamous cell carcinoma of the head and neck (SCCHN) is concurrent chemoradiotherapy with a 3-weekly cycle of cisplatin at a dose of 100 mg/m^2 (3W-CDDP/RT). In two pivotal trials (RTOG 9501 and EORTC22931), post-operative 3W-CDDP/RT showed a significant improvement in locoregional control (LRC) and disease-free survival compared with radiation therapy alone, and EORTC 22931 also showed a significant improvement in overall survival (OS) (1,2). These significant benefits of post-operative 3W-CDDP/RT were further supported by a combined analysis of RTOG 9501 and EORTC 22931 (3). However, post-operative 3W-CDDP/RT is associated with greater toxicity than post-operative radiation therapy alone and the complete delivery rate of three cycles of cisplatin and RT in prior pivotal trials was only ~60% (1,2,4).

Few prospective data for post-operative 3W-CDDP/RT in Asian populations are available, and acceptance of adjuvant chemoradiotherapy in Japan is low. Here, we evaluated the feasibility and safety of post-operative 3W-CDDP/RT in a Japanese population.

PATIENTS AND METHODS

Patient Selection

All patients had pathologically confirmed locally advanced SCCHN arising in the oral cavity, oropharynx, hypopharynx or larynx without distant metastasis and had undergone surgical resection without gross residual disease. Patients with local recurrence who underwent surgical resection with curative intent were also enrolled in this feasibility trial.

At least one of the following high-risk pathologic features was required: (1) microscopically involved (5 mm or less) resection margins, (2) extracapsular spread in at least one lymph node and (3) two or more positive lymph nodes. Additional entry criteria included age 20–75 years; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; and adequate hematologic and organ function, namely a white-cell count of at least 3500/m^3, platelet count of at least 100 000/m^3 and creatinine clearance of more than 70 ml/min. Patients with a history of previous chemotherapy or radiotherapy were excluded. The trial was conducted under a multi-institutional design in four institutions in Japan, the National Cancer Center Hospital East, Kobe University Hospital, Miyagi Cancer Center and Shizuoka Cancer Center. The study protocol was approved by the institutional review committee of each center, and all patients gave written informed consent before study entry in accordance with institutional guidelines.

Treatment Plan

All eligible patients underwent definitive surgery with curative intent. The extent of surgical resection of the primary tumor and/or neck dissection procedures followed accepted criteria for adequate excision, which depend on the volume and location of the tumor.

All patients underwent radiation therapy within 8 weeks after definitive surgery consisting of conventionally fractionated doses of 2 Gy each in 5-weekly sessions. Target-volume doses and maximal dose to the spinal cord were recorded. Treatments were conducted on linear accelerators of 4–6 MV using egocentric techniques. A large volume encompassing the primary site and all draining lymph nodes at risk received a dose of more than 40 Gy in 20 fractions over a period of 4 weeks. Regions that were adjacent to the high-risk area received a dose of more than 46 Gy in 23 fractions over a period of 4.5 weeks. Regions that were at high risk for malignant dissemination or that had inadequate resection margins received a total of 66 Gy in 33 fractions over a period of 6.5 weeks. The dose to the spinal cord was limited to 46 Gy.

Concurrent chemotherapy consisted of three courses of cisplatin 100 mg/m^2 infused on Days 1, 22 and 43 of the course of radiotherapy. Patients received prophylactic hydration and antiemetic agents. Aprepitant was approved in Japan in October 2009, and was therefore not available during the study period. We therefore recommended the use of a 5-HT3 antagonist and dexamethasone 16–20 mg on Day 1 and dexamethasone 8–16 mg on Days 2–3. Cisplatin was postponed if the absolute neutrophil count fell below 1000/mm^3 or platelet count fell below 75 000/mm^3. Cisplatin dose was decreased to 80 mg/m^2 if creatinine clearance dropped to 50–60 ml/min, and to 60 mg/m^2 if it dropped to 40–50 ml/min. Dose was also decreased with Grade 4 hematological toxicity or febrile neutropenia from 100 to 80 mg/m^2 or from 80 to 60 mg/m^2; with neurotoxicity or hearing loss Grade 2 to 60 mg/m^2 and administration was discontinued in the case of neurotoxicity or hearing loss Grade 3 or more. We routinely recommend prophylactic insertion of a percutaneous endoscopic gastrostomy (PEG) for nutrition support before chemoradiotherapy.

Follow-up

Patients were evaluated every 3 months for the first 12 months and every 4 months for the next 24 months. Adverse effects, weight and performance status were assessed at baseline, weekly for the first 8 weeks, and at all follow-up assessments, which were conducted every 3 months.

Study Design

Patients were enrolled after surgery and assigned to receive adjuvant concurrent chemoradiotherapy with cisplatin. Principal eligibility criteria were checked at enrollment.

In accordance with the intention-to-treat principle, all patients were included in all statistical analyses. The primary endpoint was treatment completion rate. Treatment completion was defined as delivery of 66 Gy radiation and a

cumulative cisplatin dose of more than 240 mg/m^2. Secondary endpoints were OS, relapse-free survival (RFS), LRC and adverse events. OS was defined as the time from initiation of chemoradiotherapy to death from any cause, and RFS as the time from initiation of chemoradiotherapy to recurrence or death from any cause. The duration of LRC was defined as the time from initiation of chemoradiotherapy to the occurrence of locoregional recurrence. Survival curves were estimated using Kaplan–Meier methods (5) and comparisons between survival curves were performed using the log-rank test. Treatment-related adverse events were scored according to the Common Toxicity Criteria of the National Cancer Institute, version 3.0, and categorized as acute (occurring within 90 days after initiation of chemoradiotherapy) or late (continuing or occurring after 90 days). We also assessed the 1-year feeding tube rate, which was defined as the proportion of patients using tube feeding 1 year after the initiation of chemoradiotherapy without recurrence.

Based on the previous trials (1,2,4), we considered the results as positive when the estimated treatment completion rate was around 60%, with adequate precision. Twenty or more patients were required to ensure that the lower limit of the one-sided 90% confidence interval (CI) of the treatment completion rate would be >43%. We therefore planned to recruit 25 patients. An interim futility analysis was conducted after 10 patients were enrolled.

All analyses were conducted using the Windows version of SPSS Statistics version 18 (IBM Corporation, NY, USA).

RESULTS

Patient Characteristics

Twenty-five patients were enrolled between August 2006 and June 2009. Patient characteristics are summarized in Table 1. By age, the 13 females and 12 males ranged from 26 to 68 years, with a median of 59 years. Eighteen patients were ECOG PS 0 and seven were ECOG PS 1. Sixteen patients had primary sites in the oral tongue, four in the hypopharynx, three in the oropharynx and one each in the larynx and oral floor. Twenty patients had locally advanced disease and five had locoregional recurrent disease. All 25 patients underwent definitive surgery with curative intent. By pathological stage, 1 patient was classified as having Stage III disease, 18 as having Stage IVA and 1 as having Stage IVB. All five patients who experienced locoregional recurrence did so after partial glossectomy for T1N0 or T2N0 disease, and all five received definitive surgery for locoregional recurrent disease. Fifteen patients received reconstruction surgery using the following reconstruction methods: free rectus abdominis flap in five, free jejunal flap in four, free anterolateral thigh flap in three and free radial forearm flap in three. Regarding high-risk features, 6 patients had a microscopically involved margin (incomplete resection: ICR), 15 had extracapsular extension (ECE) and 22 had multiple lymph node metastases (two or more lymph nodes).

Table 1. Patient characteristics ($n = 25$)

	Number of patients
Age: median (range)	59 (26–68)
Gender: female/male	13/12
PS: 0/1	18/7
Primary site	
Oral cavity	17
Oropharynx	4
Hypopharynx	3
Larynx	1
Stage	
III	1
IVA	18
IVB	1
Locoregional recurrent disease	5
High-risk features	
ICR	6
ECE	15
Multiple lymph node metastases	22
Histology: squamous cell carcinoma	
Well differentiated	13
Moderately differentiated	6
Poorly differentiated	6

ICR, incomplete resection; ECE, extracapsular extension.

Twenty patients had at least ICR or ECE and five had only multiple lymph nodes. Three of these five patients received definitive surgery for locoregional recurrent disease, while the other two had three or more lymph node metastases. The median number of metastatic lymph nodes was 4, ranging from 0 to 28.

Compliance with and Delivery of Treatment

Median interval from surgery to the initiation of chemoradiotherapy was 47 days (range 28–56 days). Median duration of radiation was 49 days (range 45–58 days) and 24 of 25 patients completed radiation therapy of up to 66 Gy in 33 fractions, as specified in the protocol. One patient was considered to have not completed radiation therapy because of an unacceptable fraction size (66 Gy in 30 fractions).

A total of 23 patients received three cycles of cisplatin and 2 received two cycles. Dose reduction of cisplatin was conducted as specified in the protocol: reduction was necessary in 7 patients in the second cycle and in 12 in third cycle due to renal impairment in 13, hearing impairment in 2, infection in 1, and prolongation of anorexia 1, patient refusal and unacceptable deviation from the protocol in 1 each. In the case with unacceptable deviation from the

protocol, the patient received a third cycle of cisplatin divided into four doses of 20 mg/m^2 each. Median relative dose intensity (RDI) of cisplatin was 0.83 (range 0.51–1.00).

Treatment completion was defined as 66 Gy radiation delivery with a cumulative cisplatin dose of more than 240 mg/m^2. A total of 20 patients met these criteria, with radiation up to 66 Gy in 33 fractions. Treatment completion rate was thus 80% and the lower limit of the one-sided 90% CI was 66%, which met the statistical criteria specified in the protocol.

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 3.0 and are listed in Tables 2 and 3. Grade 3/4 acute toxicity included mucositis (44%), dysphagia (28%), dermatitis (24%), nausea/vomiting (16%), neutropenia (32%) and anemia (36%). Grade 3/4 late toxicity included dysphagia (10%), xerostomia (5%) and osteonecrosis (5%). Twenty patients received prophylactic PEG insertion. During and within 30 days after adjuvant 3W-CDDP/RT, 17 of 20 patients used PEG for nutritional support, while 1 of 20 used total parenteral nutrition (TPN) instead of PEG and 2 of 20 did not use PEG at all. Two of five patients without PEG used a naso-gastric tube, one patient used TPN and one patient did not receive nutritional support. Finally, 84% (21/25) of patients received nutritional support during and within 30 days after adjuvant 3W-CDDP/RT. Among the disease-free patients, 3-, 6-month and 1-year feeding tube rates were 48% (10/21), 40% (6/15) and 20% (3/15), respectively. There were no major complications with the reconstruction flap and no treatment-related deaths within 30 days.

Table 2. Acute adverse events ($n = 25$)

Adverse event	Number of patients				
	Grade 1	Grade 2	Grade 3	Grade 4	% Grade 3/4
Leucopenia	4	9	12	0	48
Neutropenia	5	11	8	0	32
Anemia	5	11	6	3	36
Thrombocytopenia	14	4	0	0	0
Nausea	4	17	4	0	16
Vomiting	13	6	0	0	0
Anorexia	1	11	10	0	40
Constipation	5	3	0	0	0
Dysphagia	4	13	7	0	28
Mucositis	2	12	11	0	44
Dermatitis	9	10	6	0	24
Hearing loss	1	2	0	0	0
Taste alteration	7	18	—	—	—
Xerostomia	7	18	0	0	0
Febrile neutropenia	—	0	0	0	0
Infection	0	1	5	0	20
Creatinin	8	7	1	0	4
Heart failure	0	0	1	0	4

Table 3. Late adverse events ($n = 21$)

Adverse event	Number of patients				
	Grade 1	Grade 2	Grade 3	Grade 4	% Grade 3/4
Leucopenia	10	3	0	0	0
Neutropenia	7	2	0	0	0
Anemia	6	9	3	2	24
Thrombocytopenia	4	0	0	0	0
Dysphagia	8	7	2	0	10
Taste alteration	14	7	—	—	—
Xerostomia	8	12	1	0	5
Peripheral neuropathy	1	1	0	0	0
Hearing loss	0	2	0	0	0
Osteonecrosis	0	1	1	0	5
Creatinin	9	5	0	0	0
Infection	0	1	0	0	0
Hypothyroidism	1	0	0	0	0

Disease recurrence was observed in 14 patients, consisting of locoregional recurrence in 3, locoregional recurrence and distant metastasis in 2, and distant metastasis in 9. By site, nine cases of recurrence occurred in the lung, three in the cervical lymph nodes, one in the primary site and three in other sites.

Survival outcomes were estimated by the Kaplan–Meier method. With a median follow-up period for survivors of 39 months (range 19–56 months), 3-year LRC, RFS and OS were 74, 43 and 60%, respectively (Figures 1–3).

Univariate Analysis

Univariate analyses for LRC, RFS and OS were performed using the following variables: gender, ECOG PS, site of the primary tumor, disease status (locoregional recurrence or not), tumor cell differentiation and cumulative cisplatin dose (Table 4). Allowing for the small sample size of this Phase II feasibility study, RFS was significantly poorer when the primary site was in the oral cavity ($P = 0.038$) and in patients who received a cumulative cisplatin dose below 240 mg/m^2 ($P = 0.005$). Moreover, OS was significantly poorer in patients who received a cumulative cisplatin dose below 240 mg/m^2 ($P = 0.033$).

DISCUSSION

The current standard of care for post-operative high-risk SCCHN is concurrent chemoradiotherapy with a 3-week

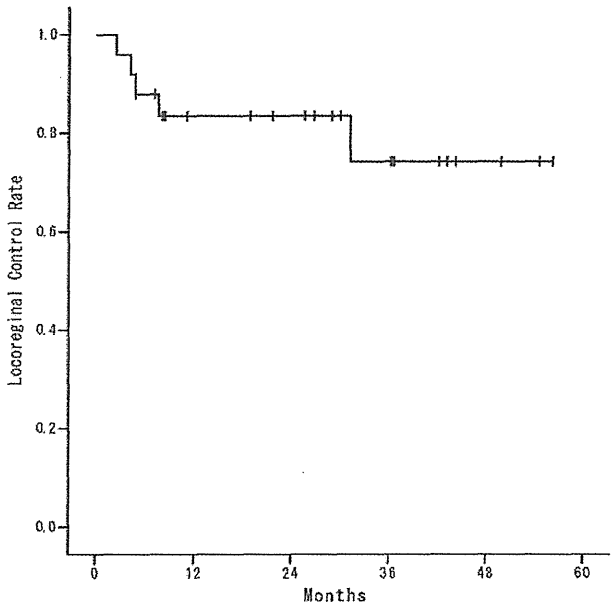

Figure 1. Kaplan–Meier estimates of locoregional control rate ($n = 25$).

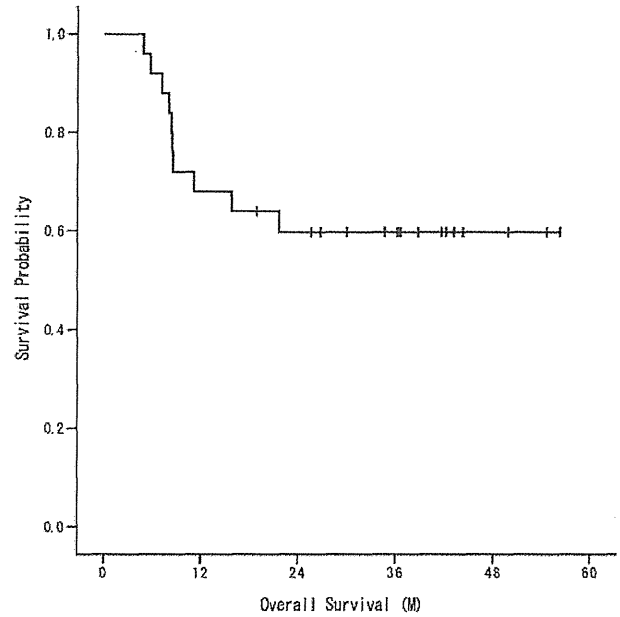

Figure 3. Kaplan–Meier estimates of overall survival ($n = 25$).

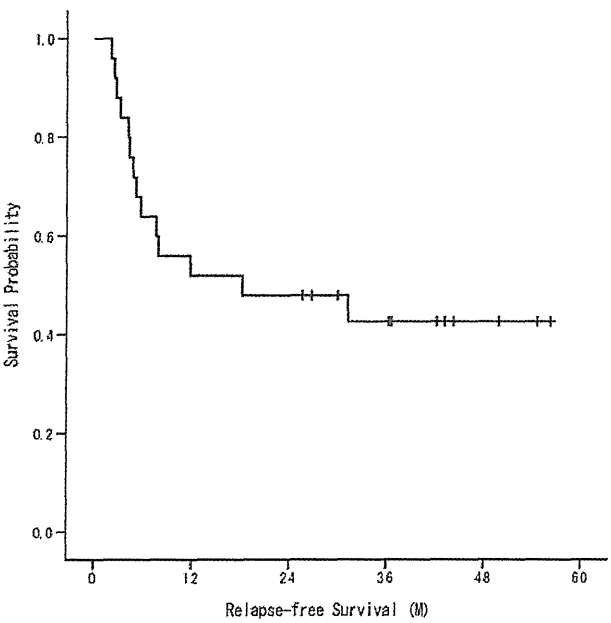

Figure 2. Kaplan–Meier estimates of relapse-free survival ($n = 25$).

cycle of cisplatin at a dose of 100 mg/m^2 (3W-CDDP/RT). In two pivotal trials (RTOG 9501 and EORTC22931), post-operative 3W-CDDP/RT showed a significant improvement in LRC and disease-free survival, and EORTC 22931 also showed a significant improvement in OS (1,2). These significant benefits of post-operative 3W-CDDP/RT were further supported by combined analysis of RTOG 9501 and EORTC 22931 (3). However, post-operative 3W-CDDP/RT is associated with greater toxicity than post-operative radiation therapy alone, and the complete delivery rate of three cycles of cisplatin and RT was only ~60% (1,2,4). This poor treatment compliance with 3W-CDDP/RT in the post-operative setting is of considerable concern. In their retrospective analysis of 3W-CDDP/RT at a reduced dose of 75 mg/m^2 in a post-operative setting, Franchin et al. (6) found that despite the reduced dose of cisplatin, only 48% (68/142) of patients were able to receive three cycles of cisplatin concurrent with radiation. Further, in their report of the safety and feasibility of 3W-CDDP/RT at a dose of 100 mg/m^2 in three nasopharyngeal cancer patients, Isobe et al. (7) concluded that 3W-CDDP/RT at 100 mg/m^2 was not tolerable for Japanese patients, while Nishimura et al. (8) recommended a dose reduction to 60–70 mg/m^2 owing to the poorer renal function of head and neck cancer patients in Japan than in western countries. In our Phase II feasibility trial, 20 patients (80%) received a total cisplatin dose of more than 240 mg/m^2 concurrent with RT and achieved an RDI of cisplatin of 0.83. Moreover, the incidence of adverse events was almost identical to that in previous pivotal trials (1,2,4) and no treatment-related deaths or severe complications with the reconstruction flap were seen. Considering that most patients (72%) were ECOG-PS 0 and the small sample size, these results indicted the tolerability and feasibility of adjuvant 3W-CDDP/RT for Japanese patients with post-operative high-risk SCCHN.

Against this, the relatively high incidence and severity of acute toxicities of 3W-CDDP/RT are also of concern. Among these, G3/4 hematological toxicities were seen in around 40% of patients who received with 3W-CDDP/RT (1,2,9). In our Phase II trial, 32% (8/25) of patients

Table 4. Univariate analysis for survival ($n = 25$)

	No. of patients	Three-year locoregional control rate (%)	*P* value	Three-year RFS (%)	*P* value	Three-year OS (%)	*P* value
Gender							
Female	13	79.1	0.399	59.3	0.09	69.2	0.281
Male	12	74.1		25.0		50.0	
ECOG PS							
0	18	70.7	0.721	42.9	0.663	66.2	0.307
1	7	85.7		42.9		42.9	
Site of primary tumor							
Oral cavity	17	58.8	0.987	23.5	0.038	46.3	0.055
Other	8	75.0		75.0		87.5	
Disease status							
Locally advanced disease	20	75.0	0.784	48.9	0.157	65.0	0.29
Locoregional recurrent disease	5	80.0		20.0		40.0	
Tumor differentiation							
Well or moderately differentiated	19	65.5	0.176	39.5	0.835	62.7	0.48
Poorly differentiated	6	100		50.0		50.0	
Cumulative cisplatin dose							
$\geq$240 mg/m^2	22	76.3	0.36	48.5	0.005	68.2	0.033
<240 mg/m^2	3	66.7		0		0	

LRCR, locoregional control rate; RFS, relapse-free survival; OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group performance status.

experienced G3/4 neutropenia. These may lead to infection at the surgical site after definitive surgery for advanced SCCHN. Moreover, 32% (8/25) of patients experienced Grade 2 or more serum creatinin elevation, and decreases in creatinin clearance led to a dose reduction of cisplatin in 52% (13/25) of patients. Given the suggested association between efficacy and total dose of cisplatin in concurrent chemoradiation for SCCHN (10–12), administration with a view to minimal renal impairment is important in maintaining the efficacy of concurrent chemoradiotherapy with cisplatin. Attempts to improve treatment compliance and safety in the adjuvant setting have also resulted in the investigation of weekly cisplatin concurrent with radiation (W-CDDP/RT) (13–16). In this regard, we are now planning a Phase III trial of adjuvant chemoradiotherapy comparing weekly with 3-weekly cisplatin in post-operative high-risk patients with SCCHN.

With regard to efficacy, 3-year RFS and OS after a median follow-up period for survivors of 39 months were 43 and 60%, respectively. In RTOG 95-01, 3-year event-free survival and OS were 47 and 56% (1), while 5-year event-free survival and OS in EORTC 22 931 were 47 and 53% (2), respectively. Considering that our present data included cases with local recurrence, survival in our study appears identical with the results of these previous pivotal Phase III trials (1,2).

In univariate analysis, prognosis appeared to be poorer in patients with oral cavity cancer and those who received a cumulative cisplatin dose of <240 mg/m^2. Three-year RFS and OS for patients with oral cavity cancer were 23.5 and 46.3%, respectively. The poor prognostic significance attached to oral cavity cancer is well known (17–20), and our present results appeared consistent with these previous reports. In contrast, the relationship between cumulative cisplatin dose and the efficacy of chemoradiotherapy has been a matter of debate. From their analysis of previous trials (10–12), Ang et al. noted that a cumulative cisplatin dose of ~200 mg/m^2 might be sufficient to yield a beneficial antitumor effect, independently of schedule. These authors also reported that LRC was significantly worse in patients receiving two cycles of cisplatin than in those receiving three [hazard ratio (HR): 1.7, 95% CI: 1.20–2.54] and that OS with only a single cycle was significantly worse than that with three cycles (HR: 2.1, 95% CI: 1.35–3.32) (21). Our data also suggested that survival outcome deteriorated with a cumulative cisplatin dose below 240 mg/m^2, which may suggest the superiority of continuing cisplatin cycling for as long as possible.

In conclusion, this is the first Phase II feasibility trial of adjuvant chemoradiothrapy with 3-weekly cisplatin for post-operative high-risk patients with SCCHN in a Japanese population. This treatment was feasible and had an identical safety profile to those in pivotal Phase III trials. Oral cavity

cancer and a cumulative cisplatin dose below 240 mg/m^2 appeared to be associated with a poor survival outcome.

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Conflict of interest statement

None declared.

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Induction Chemotherapy with Docetaxel, Cisplatin and S-1 Followed by Proton Beam Therapy Concurrent with Cisplatin in Patients with T4b Nasal and Sinonasal Malignancies

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Objective: For the treatment of patients with T4b nasal and sinonasal malignancies, definitive chemoradiotherapy was contraindicated due to the risk of brain damage and blindness. However, combination chemotherapy with docetaxel, cisplatin and S-1 is well tolerated and effective. We conducted a retrospective analysis to evaluate the efficacy and feasibility of induction chemotherapy using docetaxel, cisplatin and S-1 followed by proton beam therapy concurrent with cisplatin.

Methods: Thirteen patients treated with docetaxel, cisplatin and S-1 were analyzed. Docetaxel, cisplatin and S-1 consisted of 60–70 mg/m^2/day docetaxel on day 1, 70 mg/m^2/day cisplatin on day 1 and 60–80 mg/m^2/day S-1 on days 1–14. Treatment was repeated every 3–4 weeks with a maximum number of three treatment cycles. According to the response to docetaxel, cisplatin and S-1, patients received either proton beam therapy concurrent with 20 mg/m^2/day cisplatin on days 1–4 every 3 weeks or proton beam therapy alone.

Results: Neutropenia represented the most common Grade 3/4 hematological toxicity (76.9%), while the most frequently observed non-hematological toxicity was nausea (23.0%). After the completion of docetaxel, cisplatin and S-1, the overall response rate was 38.4% (5 of 13), with 1 patient achieving complete response and 4 patients achieving partial response. Subsequently, 10 patients received proton beam therapy concurrent with cisplatin, 2 received proton beam therapy alone and 1 received palliative radiation. No severe toxicity was observed during proton beam therapy. After the completion of proton beam therapy, 11 patients (84.6%) achieved complete response and no brain damage or blindness occurred.

Conclusions: Induction chemotherapy with docetaxel, cisplatin and S-1 followed by proton beam therapy concurrent with cisplatin is well tolerated and displays promising antitumor activity that warrants further investigation.

Key words: nasal – sinonasal – induction chemotherapy – proton – head and neck

INTRODUCTION

Nasal and sinonasal malignancies are rare, representing only 3–5% of all head and neck cancers (HNC) (1,2). Although a variety of malignancies arise in this region, squamous cell carcinoma is most frequent, followed by adenocarcinoma and adenoid cystic carcinoma (3). As the nasal and sinonasal regions have limited anatomical access and permit the asymptomatic growth of malignancies, most patients first realize symptoms when tumors reach a large size or invade the surrounding normal critical organs, and are often initially diagnosed with unresectable disease (4). These patients are not candidates for gross total resection and are typically treated with either definitive radiotherapy or concurrent chemoradiotherapy. However, due to the proximity of critical organs to malignancies in the nasal and sinonasal sinuses, 15–30% of the patients develop radiation-induced serious complications, including brain necrosis, hearing loss, meningitis, unilateral or bilateral blindness, optic neuritis, cataracts, osteoradionecrosis and central nervous system damage (5–7). Despite the use of radiotherapy with or without chemotherapy, outcomes are often poor in these patients due to the high occurrence of local relapse, as reflected in the reported 5-year overall survival (OS) rate of only 15% (8).

To reduce radiation-induced toxicity and improve treatment outcomes for locally advanced nasal and sinonasal malignancies, we previously evaluated two treatment strategies involving induction chemotherapy (IC) and proton beam therapy (PBT) (9). In the first approach, we demonstrated that IC led to reduced tumor sizes and avoided brain damage and ocular/visual toxicity that often results from radiotherapy (9). We also examined IC with irinotecan plus docetaxel (ID) for olfactory neuroblastoma, but the relatively poor treatment outcomes suggested that ID was not a suitable approach (9). We subsequently performed a Phase I clinical study of IC with docetaxel, cisplatin and S-1 (TPS) and found that this treatment was well tolerated, feasible and showed a good antitumor activity with locally advanced HNC, which included several nasal and sinonasal malignancies (10). As the response rate to TPS was 70%, IC combined with TPS appears to be a superior approach than IC with ID.

In addition to IC, we have also evaluated the use of PBT for the treatment of nasal and sinonasal malignancies (11,12). PBT was anticipated to improve tumor local control probability and decrease acute and late toxicities of the surrounding normal tissue (13–15). A previous retrospective analysis of 14 patients with olfactory neuroblastoma from our institute who were treated with PBT displayed excellent local control and survival outcomes without serious adverse effects, suggesting that PBT allows the delivery of tumoricidal doses with minimal complications (11).

Here, we conducted a retrospective analysis to evaluate the efficacy and feasibility of IC with TPS followed by PBT concurrent with cisplatin for the treatment of T4b nasal and sinonasal malignancies.

PATIENTS AND METHODS

Patients

We reviewed the case records of 13 patients who were treated for T4b nasal and sinonasal malignancies at the 'Search' between January 2006 and March 2012. Tumor staging in the present study was evaluated based on sections of the nasal cavity and sinonasal sinuses using the TNM classification of the UICC 6th edition, regardless of the histology type.

Treatment Plan

Induction Chemotherapy

Patients received three cycles of TPS chemotherapy followed by PBT concurrent with cisplatin. The chemotherapy regimen consisted of a 1 h infusion of docetaxel at 60–70 mg/m^2/day on day 1, a 2 h infusion of cisplatin at 70 mg/m^2/day on day 1 and S-1 twice daily on days 1–14 at 60–80 mg/m^2/day. The treatment was repeated every 3–4 weeks with a maximum number of three treatment cycles. Ciprofloxacin was administered as a prophylactic on days 5–15.

Chemotherapy Concurrent with PBT

After the completion of TPS, patients received PBT concurrent with cisplatin, which was administered at 20 mg/m^2 daily for 4 days. The treatment was repeated every 3 weeks with a maximum of three treatment cycles. The total dose of PBT was 65 cobalt Gray equivalents (GyE) for 4–5 fractions per week in 2.5 GyE once-daily fractions.

PBT planning was performed using a three-dimensional computed tomography (CT) planning system. In this system, the proton beam was generated using a Cyclotron C235 with an energy of 235 MeV at the exit. Relative biologic effectiveness was defined as 1.1, based on our preclinical experiments (16). Dose distribution was optimized using the spread-out Bragg peak method and obtained using a broad-beam algorithm.

Gross tumor volume (GTV) was determined by examination using CT, magnetic resonance imaging (MRI) and/or positron emission tomography-CT. Clinical target volume (CTV) was defined as the GTV plus a 5 mm margin and the sinuses adjacent to the GTV. In cases of tumor invasion into the brain, the area of T2 prolongation on MRI was also included in the CTV. Planning target volume (PTV) was basically defined as the CTV plus a 3 mm margin, but was finely adjusted where necessary in consideration of organs at risk. Beam energies and spread-out Bragg peaks were fine-tuned such that the PTV was minimally covered by a 90% isodose volume of the prescribed dosage. The irradiated dose was minimized by the delivery of the proton beam with two or three beam arrangements.

Elected nodal irradiation was not planned because of the low incidence of lymph node metastases in these diseases.

Evaluations

Pretreatment evaluation consisted of complete history and physical examinations, complete blood counts, liver function tests, chest X-rays and ECGs. All patients were imaged with CT and MRI scans of the head and neck. Bone scans and CT scans of the abdomen or chest were performed when clinically indicated. Treatment responses were assessed radiographically according to RECIST 1.0 criteria after the third cycle of chemotherapy and on the completion of chemoradiotherapy. The National Cancer Institute Common Toxicity Criteria (version 3.0) was used to describe chemotherapy- and chemoradiation-related toxicities.

Statistical Methods

The follow-up time for each patient was calculated as the time from the start of treatment to 31 March 2012. A survival curve was estimated using the Kaplan–Meier method. Safety and efficacy analyses were both conducted on an intention-to-treat population, defined as all patients enrolled in the study who received at least one dose of chemotherapy. Progression-free survival (PFS) was calculated from the date of the first administration of chemotherapy to the first documentation of disease progression, subsequent therapy or death. OS was determined from the date of the first administration of chemotherapy to the date of death or the last confirmation of survival. Statistical data were obtained using the SPSS software package (SPSS 11.0 Inc. Chicago, IL, USA).

RESULTS

Patient Characteristics

The clinical and disease characteristics of the 13 patients with histologically proven tumors examined in this retrospective analysis are summarized in Table 1. The median patient age was 47 years (range, 28–60 years). The primary tumor sites involved the nasal cavity (9 of 13) and ethmoid sinus (4 of 13). The leading histology was olfactory neuroblastoma. No patients had clinical or pathologic evidence of neck disease at the time of initial treatment.

Nine patients (69%) completed the three cycles of planned IC. Three patients who were refractory to IC did not receive the third cycle of IC, while one patient received only one cycle due to disease progression. Ten patients received PBT concurrent with cisplatin and two patients received PBT alone, while the patient who experienced disease progression during IC received palliative radiotherapy.

Table 1. Patient characteristics

Characteristic	No. of patients ($n = 13$)
Age (years)	
Median	47
Range	28–60
Sex	
Male	9
Female	4
ECOG performance score	
0	13
Site of primary tumor	
Nasal cavity	9
Ethmoid sinus	4
Histology	
Olfactory neuroblastoma	7
Squamous cell carcinoma	3
Adenocarcinoma	1
Undifferentiated carcinoma	1
Small cell carcinoma	1

Table 2. Toxicities experienced during induction chemotherapy

Toxicity	No. of patients ($n = 13$)				Percent Grade 3–4
	Grade				
	1	2	3	4	
Hematological toxicity					
Leukopenia	1	7	5	0	38.4
Neutropenia	0	2	4	6	76.9
Febrile neutropenia	0	0	0	0	0
Anemia	8	5	0	0	0
Thrombocytopenia	5	2	0	0	0
Non-hematological toxicity					
Nausea	6	2	3	0	23.0
Vomiting	2	4	0	0	0
Anorexia	7	6	0	0	0
Mucositis	2	0	0	0	0
Diarrhea	2	0	0	0	0

Adverse Events

The acute toxicities experienced during the TPS treatment are listed in Table 2. Although 10 patients (76.9%) experienced Grade 3 or 4 neutropenia and 3 patients (23.0%) experienced Grade 3 nausea, toxicity was as expected and manageable.

Acute toxicity scores of chemoradiotherapy are summarized in Table 3. Two patients (16.6%) experienced Grade 3 mucositis, which developed on the hard palate and to a lesser degree on the cheek and pharynx. Interference with

Table 3. Toxicities experienced during proton beam therapy

Toxicity	No. of patients ($n = 12$)				Percent Grade 3–4
	Grade				
	1	2	3	4	
Hematological toxicity					
Leukopenia	9	3	0	0	0
Neutropenia	0	1	0	0	0
Febrile neutropenia	0	0	0	0	0
Anemia	8	4	0	0	0
Thrombocytopenia	5	0	0	0	0
Non-hematological toxicity					
Mucositis	0	1	2	0	16.6
Anorexia	4	5	0	0	0
Nausea	4	3	0	0	0
Vomiting	2	0	0	0	0
Infection	0	0	0	0	0

nutrition was minor, and no patients required a feeding tube. No brain damage or blindness was recorded. In addition, late toxicities were not observed at the time of March 2012.

Treatment Outcomes

Efficacy data for the TPS therapy are listed in Table 4. All patients enrolled in the present study were assessable for a response to TPS. Objective response rate (ORR) was documented in five patients (38.4%), including one patient with complete response (CR) and four with partial responses (PRs) after the IC of TPS (Figs 1 and 2). After the completion of chemoradiotherapy, ORR was documented in 12 patients (92.3%), including 11 with CR and 1 with PR. Each ORR to TPS according to the histology was 14.2% for patients with olfactory neuroblastoma, 33.3% for patients with squamous cell carcinoma and 100% for patients with others.

The median follow-up time was 56.5 months (range, 0.6–63.5months), and the 5-year PFS and OS were 33.8 and 75.5%, respectively. Eight of the 13 patients were alive at the time of this report with no evidence of disease, while 2 patients were alive with disease. Two patients died due to local disease progression and one died as a result of distant metastasis.

Local relapse developed in three patients. The median time to local relapse was 14.4 months (range, 0.3–25.1 months). Relapses occurred within the irradiated region in two patients and on the margin of the irradiated region in one patient. Of the three patients with local relapses, two subsequently died of their disease, while one patient is presently alive with disease and continue to receive chemotherapy. Regional relapse developed in four patients; two of

Table 4. Treatment outcomes

CR	PR	SD	PD	RR (%)	95% CI
Induction chemotherapy ($n = 13$)					
1	4	7	1	38.4	17.7–64.4
IC → PBT with cisplatin[a] or palliative RT					
11	1	0	1	92.3	66.6–98.6

CR, complete response; PR, partial response; PD, progression disease; RR, response rate; SD, stable disease.
[a]Two patients did not receive cisplatin due to refractory disease following TPS.

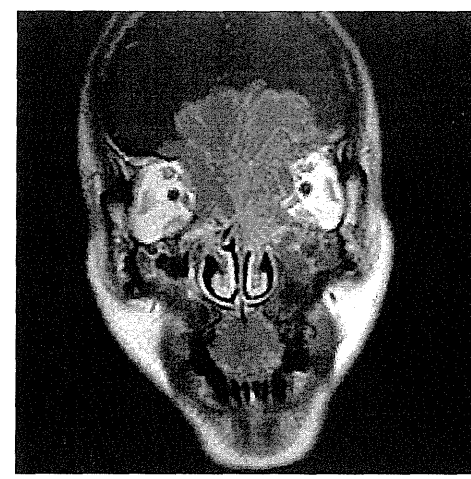

Figure 1. Coronal magnetic resonance imaging (MRI) of a patient with a T4b squamous cell carcinoma in the nasal cavity, with invasion of the orbit and intracranial extension.

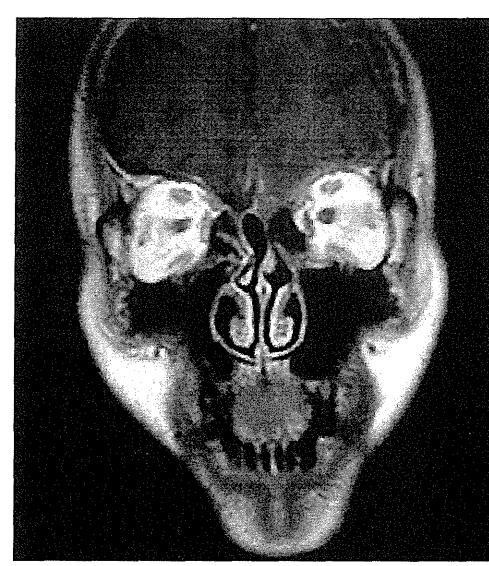

Figure 2. The MRI was repeated after three cycles of docetaxel, cisplatin and S-1, demonstrating a complete response.

these patients are presently alive with disease, while two patients who underwent elective neck dissection are alive with no relapse. Finally, one patient developed distant metastasis to meninges 9.1 months after the start of treatment and was dead with disease.

DISCUSSION

In the present retrospective study, we evaluated the efficacy of IC using TPS followed by PBT concurrent with cisplatin. Of the 10 patients who received PBT concurrent with cisplatin, 9 patients (90%) achieved CR, and the 5-year OS rate was 77.7%, with no brain damage or blindness recorded. Our study suggests that IC with TPS followed by PBT concurrent with cisplatin is well tolerated and displays reducing complication and promising antitumor activity.

The efficacy of chemotherapy for nasal and sinonasal malignancies is unclear (5), as it is generally used for palliative treatment of advanced or recurrent disease. However, favorable responses obtained with various chemotherapeutic regimens have prompted several institutions to modify standard therapeutic approaches in an attempt to improve treatment outcomes. Recently, chemotherapy has been evaluated as part of multimodality therapy delivered in either induction or concomitant settings (17,18). For example, Licitra et al. (17) reported the retrospective analysis of 49 patients with resectable sinonasal cancer who were treated with IC (cisplatin, fluorouracil and leucovorin) followed by surgery and post-operative radiotherapy. The objective response to IC and 3-year OS were 43 and 69%, respectively, suggesting that IC may play a role in surgery-sparing treatment approaches. In a similar study, Lee et al. (18) reported that a subgroup of 16 patients with Stage III or IV sinonasal carcinoma who received IC consisting of three cycles of cisplatin and fluorouracil achieved an 87% clinical response, indicating that IC could be an avenue for further improving the suboptimal results often encountered with reductions in tumors in close proximity with important structures. In the present retrospective study, after the completion of TPS, the overall response rate was 38.4% (5 of 13), with one patient achieving CR and four patients achieving PR. Neutropenia was the most common Grade 3 and 4 hematological toxicity (76.9%), while the most frequently observed non-hematological toxicity was nausea (23.0%). IC of TPS was well tolerated, feasible and showed good antitumor activity, which enabled the reduction in large tumor masses without severe toxicity.

Although squamous cell carcinoma is the most frequent pathology of HNC, olfactory neuroblastoma was most often observed in the present study. We speculate that the dominance of olfactory neuroblastoma among patients was due to referrals from institutions in the surrounding area with limited experience treating this type of carcinoma. Rosenthal et al. (19) reported that patients with olfactory neuroblastoma had excellent local and distant control rates with local therapy alone, but found higher rates of systemic failure for patients with neuroendocrine carcinoma, undifferentiated sinonasal carcinoma and small cell carcinoma. Although data concerning the response of nasal and sinonasal malignancies to IC are limited, several authors have reported the effectiveness of chemotherapy in the treatment of olfactory neuroblastoma, squamous cell carcinoma, undifferentiated carcinoma and adenocarcinoma. In the present study, about half of the patients had olfactory neuroblastoma, and the response rate after the completion of IC followed by PBT concurrent with cisplatin was high. This further emphasizes the need for accurate pathologic diagnosis of nasal and sinonasal malignancies, which may allow the use of separate IC as dictated by the histological analyses.

PBT approaches that would allow decreased irradiation doses to the surrounding critical organs while simultaneously delivering curative high-dose irradiation doses to tumors is critical for minimizing severe complications (5–7). Improvements of local control rates in treatment plans with lower doses to critical organs have been demonstrated when proton plans have been compared with photon plans in patients with nasal and sinonasal malignancies (13–15). Weber et al. (20) examined the long-term toxicity in patients with advanced sinonasal malignancies treated with proton/photon accelerated fractionated radiation and found that at a median dose of 69.6 GyE, 5.6% of the patients developed Grade 3 late visual/ocular toxicity, and no Grade 4–5 late visual/ocular toxicity, vascular glaucoma, retinal detachment or optic neuropathy were observed. Our group previously examined the clinical outcomes of 39 patients with unresectable malignancies treated with PBT at our institution between 1999 and 2006 and demonstrated that most patients experienced Grade 1–2 dermatitis in the acute phase, and 5 patients (12.8%) experienced Grade 3 or greater were observed (12). In the present study, 12 patients received PBT and no brain damage or blindness was recorded. When radiation is combined with concurrent chemotherapy, the acute and long-term side effects are occasionally more pronounced, and greater care and attention to the dose to normal surrounding organs is required for preventing complications. In the present study, 10 patients received PBT concurrent with cisplatin and no brain damage or blindness was recorded, suggesting that IC led to reduced tumor size and PBT could allow the delivery of tumoricidal doses with minimal complications.

Several limitations of the study warrant mention. First, this study includes the inherent limitations of a retrospective study. Second, only a small number of patients with biased histological types of cancer were examined. Here, sufficient doses of chemoradiotherapy without severe complications were achieved using IC and PBT; however, we cannot make definitive conclusions regarding the safety or side effect because of these limitations. Although it is difficult to conduct a prospective study as nasal and sinonasal malignancies are rare, additional patients are needed to confirm these results.

In conclusion, our retrospective analysis revealed that IC with TPS followed by PBT concurrent with cisplatin was well tolerated and effective in patients with locoregionally advanced malignancies of the nasal cavity and paranasal sinuses. This treatment approach demonstrated promising activity and minimal toxicity to warrant Phase II testing and may represent a suitable substitute for chemoradiotherapy alone for patients with T4b nasal and sinonasal malignancies.

Conflict of interest statement

None declared.

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ORIGINAL ARTICLE

A Dermatitis Control Program (DeCoP) for head and neck cancer patients receiving radiotherapy: a prospective phase II study

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Abstract
Purpose We speculated that a systematic program to manage radiation dermatitis might decrease the incidence of severe or fatal cases in head and neck cancer patients receiving radiotherapy. Here, we conducted a prospective phase II study to clarify the clinical benefit of a Dermatitis Control Program (DeCoP) that did not use corticosteroids.
Patients and methods Head and neck cancer patients scheduled to receive definitive or postoperative radiotherapy were enrolled. Radiation dermatitis was managed with a DeCoP consisting of a three-step ladder: Step 1, gentle washing; Step 2, gentle washing and moistening of the wound-healing environment; Step 3, prevention against infection, gentle washing and moistening of the wound-healing environment. The primary endpoint was the incidence of grade 4 dermatitis.
Results A total of 113 patients were registered between January 2009 and February 2010. Eighty patients received radiotherapy as an initial approach, while the remaining 33 received radiotherapy postoperatively. Grade 3 and 4 dermatitis events occurred in 11 (9.7%) and 0 (0%, 95% confidence interval 0–3.2%) patients, respectively. Median radiation dose at the onset of grade 2 dermatitis was 61.5 Gy (range 36–70 Gy) and median period between onset and recovery was 14 days (range 1–46 days).
Conclusion The Dermatitis Control Program has promising clinical potential. Radiation dermatitis might be manageable if gentle washing and moistening of the wound-healing environment is done.

Keywords Head and neck cancer · Cancer nursing · Dermatitis · Radiotherapy

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Introduction

Chemoradiotherapy is now commonly used in the treatment of head and neck cancer. For example, single-agent cisplatin concurrent with radiotherapy is now the nonsurgical standard care for locally advanced squamous cell carcinoma of the head and neck (SCCHN) patients [1–3], and is also considered the standard adjuvant therapy for high-risk postoperative patients [4–6]. Recently, induction chemotherapy using cisplatin, 5-fluorouracil, and docetaxel followed by chemoradiotherapy has shown promise for locally advanced head and neck cancer patients at high risk of distant metastases [7, 8].

However, as treatment strength increases, so too does the risk of toxicity. Acute skin reactions like radiation dermatitis are common, and not only risk interrupting treatment but can even be fatal. Although various topical medications have been used to manage and treat radiation dermatitis, there remains no agreement on the best treatment plan [9, 10].

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Among those being considered, there is strong evidence supporting the efficacy of a simple treatment plan that involves only gentle washing and moistening of the wound-healing environment [11, 12]. Here, we describe a prospective phase II study that uses a Dermatitis Control Program (DeCoP) incorporating a three-step plan, which includes gentle washing and moistening of the would-healing environment but no corticosteroid use, for head and neck patients receiving radiotherapy.

Patients and methods

This single institution prospective phase II study was approved by the institutional review board of the National Cancer Center Hospital before the start of patient enrollment. This trial was registered with UMIN-clinical trials registry (UMIN-CTR: UMIN000001579).

Eligibility

Patients fulfilling the following criteria were enrolled: histologically confirmed SCCHN; 20–75 years of age; Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 2; normal organ function; and scheduled to receive definitive or postoperative radiotherapy (>50 Gy). Written informed consent for treatment was obtained from all patients before its initiation.

Treatment

The main protocol was the 'Dermatitis Control Program'. This systematic program consists of a three-step ladder (Table 1).

Supportive treatment for grade 0–1 radiation dermatitis (Step 1)

The basic concept of this step is 'watchful waiting'.

All treatments for radiation dermatitis prevention except gentle washing were avoided. All patients were instructed on how to wash with lukewarm water and mild soap for routine care. Physicians or expert nurses observed each patient for dermatitis at least twice a week.

Table 1 Dermatitis Control Program steps

	Dermatitis grade (CTCAE ver. 3.0)			
	0	1	2	3
Step 1: Gentle wash	○	○	○	○
Step 2: Moistened wound environment		Δ	○	○
Step 3: Infection prevention		Δ	Δ	○

○, Treatment done unconditionally; Δ, treatment done if feasible

Supportive treatment for grade 2 radiation dermatitis (Step 2)

The basic concept of this step is 'minimally required intervention'. The irradiated area was covered with gauze and moistened with either vaseline or dimethyl isopropyl-azulene. All outpatients and their families were instructed on how to cover and moisten the irradiated area. For inpatients, gauze coating was done by the patient or nurse. An example of Step 2 is shown in Fig. 1.

Supportive treatment for grade 3–4 radiation dermatitis (Step 3)

The basic concept for this step is similar to that of Step 2 except for the use of preventative action against infection. Physicians or experts including wound, ostomy, and continence nurses observed for dermatitis every business day. If no infection was noted, antibiotic drugs were not administered.

Toxicity

Adverse events related to acute toxicity by radiotherapy or chemoradiotherapy were coded according to the common terminology criteria of adverse events, version 3 (CTCAE ver. 3.0). According to these criteria, grade 2 radiation dermatitis includes moderate to brisk erythema, patchy moist desquamation mostly confined to skin folds and creases, and moderate edema. Grade 3 radiation dermatitis consists of moist desquamation other than skin folds or creases and bleeding induced by minor trauma or abrasion.

Radiation dermatitis was evaluated by physicians or nurses based on dermatitis grading according to the CTCAE ver. 3.0, followed by DeCoP performed according to the grading. The investigators' gradings were subsequently evaluated by a central review committee using photographs.

Irradiation methods

Irradiation dose and modality (conventional radiotherapy, intensity-modulated radiotherapy or proton beam therapy) varied according to primary site and tumor stage. Full-face immobilization (thickness 2 mm) was used for all patients to minimize set-up error. Target volumes were defined in accordance with International Commission on Radiation Units and Measurements Reports 50 and 62.

Treatment evaluation and statistical analysis

The primary endpoint of this study was the incidence of grade 4 dermatitis. Skin breakdown has the potential for

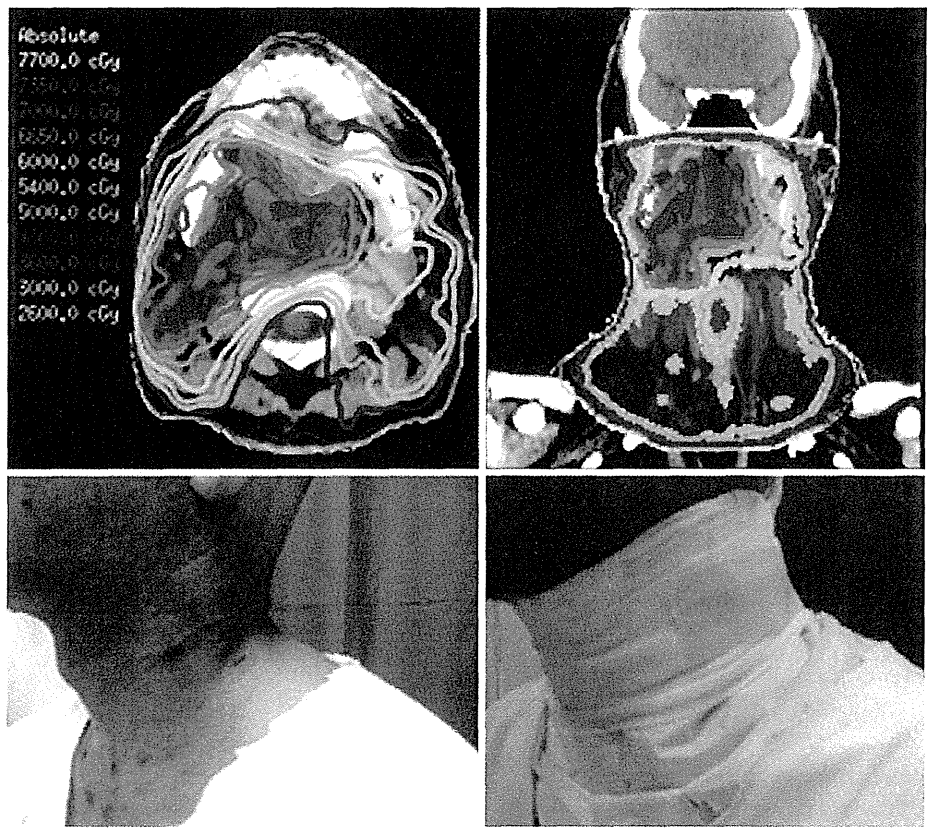

Fig. 1 Dermatitis Control Program Step 2. The case was a 44-year-old-male with T4N2cM0 oro-pharyngeal cancer. He was treated with induction chemotherapy followed by chemoradiotherapy. The irradiated area was covered with gauze and moistened with dimethyl isopropylazulene. It is very important that not only the physicians but also the co-medical staff understand where the radiation field is

infection, which risks disrupting radiotherapy treatment. Unplanned disruption was defined as one or more days of interruption, excluding weekends or days for planned machine maintenance.

If the true rate of grade 4 dermatitis was 7% or less and the true rate of disruption was less than 16%, the DeCoP was applied. To conduct statistical analysis with 90% power and a one-sided type-I error of 5%, a minimum of 104 patients were needed. However, we assumed that 15% of our patients would ultimately be excluded from analysis due to violation of the protocol or other reasons, and thus estimated that 120 patients were needed.

Descriptive statistics, including mean, standard deviation, median, range, and percentage, were used to describe patient demographics, and pathological and clinical characteristics.

Results

Patient characteristics

One hundred and twenty patients were registered between January 2009 and February 2010. Seven patients were excluded from analysis due to a change in treatment strategy (surgery for three patients, palliation for three patients) and refusal to participate after registration (one patient). The remaining 113 patients are characterized in Table 2.

With regard to treatment strategy, 80 patients (71%) received radiotherapy as an initial approach, and the remaining 33 (29%) in a postoperative setting. The major combination chemotherapy regimen was cisplatin alone (53/113, 47%).

Treatment compliance

All patients received the planned radiotherapy without any dose reduction. The rate of unplanned breaks in radiotherapy was 10.6% (12/113) owing to acute toxicity (two patients), PEG trouble (one patient), emergency tracheostomy (one patient), infection (three patients), unplanned machine trouble (one patient), patient discretion (two patients), and other reasons (two patients). Of these, the median interval of radiation interruption was 4 days (range 1–5 days), and no unplanned break of more than 1 week occurred.

Toxicity

The toxicity profile during radiotherapy/chemoradiotherapy is shown in Table 3. No fatal hematological events occurred.

Table 2 Patient characteristics

Characteristics	*n*
No. of patients	113
Age, years	
Median (range)	63 (22–87)
Gender	
Male/female	93/20
Performance status	
0–1/2	99/14
Primary site	
Naospharynx	13
Oropharynx	23
Hypopharynx	18
Larynx	33
Tongue, oral cavity	12
Unknown	14
Radiotherapy setting	
Postoperative RT	33
Definitive RT	80
Treatment strategy	
IC → CRT	25
CRT	43
RT alone	45
Radiation dose, Gy	
Median (range)	70 (54–70)
Combination	
Cisplatin alone	53
Chemotherapy	
Cisplatin and 5-FU	11
Cisplatin and S-1	2
Other platinum	1

CRT Chemoradiotherapy, *IC* induction chemotherapy, *RT* radiotherapy, *5-FU* 5-fluorouracil

Mucositis and dermatitis were the most common non-hematological toxicities.

Grade 2 and 3 dermatitis events were seen in 63 (56%) and 11 (9.7%) patients, respectively. No grade 4 dermatitis events were seen (0%, 95% confidence interval 0–3.2%). Median time until the onset of grade 2 dermatitis was 43.5 days (range 23–60 days) and the median radiation dose at onset was 61.5 Gy (range 36–70 Gy). Median period between onset and recovery was 14 days (range 1–46 days) and the median time until recovery from the initiation of radiotherapy was 57 days (range 39–91 days) (Fig. 2).

Grade 3 mucositis events in the categories 'clinical exam' and 'functional/symptomatic' occurred in about half of the patients for each. Weight loss was recorded in 22 grade 2 patients, but not in any grade 3 patients. No treatment-related deaths occurred.

Table 3 Toxicity

	Dermatitis grade (CTCAE ver. 3.0)				
	1	2	3	4	% 3 and 4
Leucopenia	23	34	4	1	4.4
Neutropenia	71	20	1	1	1.8
Anemia	13	30	1	2	2.7
Thromobocytopenia	16	6	3	0	2.7
Nausea	23	26	5	0	4.4
Mucositis					
CE	11	56	42	1	38.1
FS	15	44	47	0	41.6
Xerostomia	14	60	2	0	1.8
Dermatitis	39	63	11	0	9.7
Febrile neutropenia	–	–	1	0	0.9
Weight loss	19	22	0	0	0

CE Clinical exam, *FS* functional/symptomatic

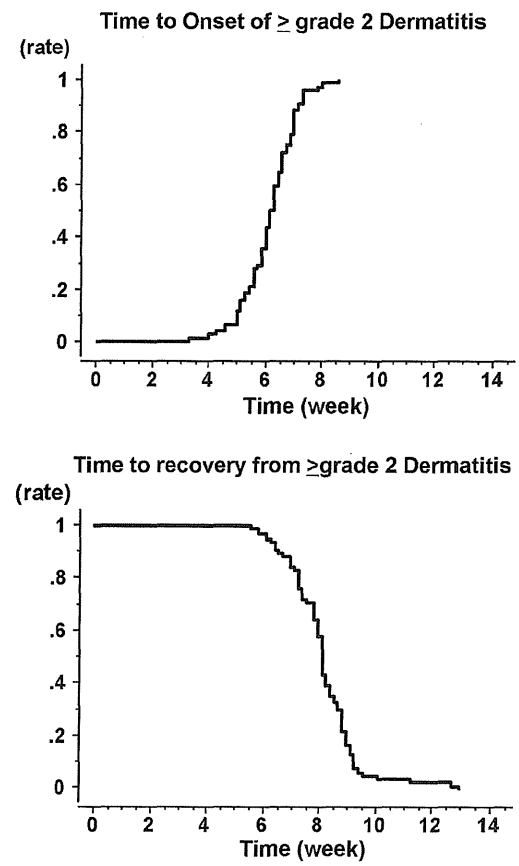

Fig. 2 Time to onset (upper) and recovery (lower) of > grade 2 dermatitis. Median time to onset of grade 2 dermatitis from the initiation of radiotherapy was 43.5 days (range 23–60 days), and median radiation dose at onset was 61.5 Gy (range 36–70 Gy). In several cases, dermatitis became worse after the end of treatment. Median time to recovery from grade 2 dermatitis from the initiation of radiotherapy was 57 days (range 39–91 days). Recovery did not take more than 6 weeks in any case

DeCoP data

All 113 patients received the planned dose of radiotherapy. The median radiation dose was 70 Gy (range 60–70 Gy) and the median duration of radiotherapy treatment was 49 days (range 33–63 days).

The frequency of using either Steps 2 or 3 to control dermatitis during radiotherapy was 63% (71/113), while at 2 weeks and 1 month after the end of radiotherapy it was 19% (21/113) and 2% (2/113), respectively.

Discussion

The primary endpoint of this study was the incidence of grade 4 dermatitis, which did not occur in any patient (0%, 95% confidence interval 0–3.2%). Grade 2 and 3 dermatitis events were seen in 63 (56%) and 11 (9.7%) patients, respectively. Given that radiotherapy is contraindicated in the presence of grade 4 dermatitis, these findings suggest that our DeCoP has good clinical potential.

To date, two randomized trials [11, 13] have assessed the effectiveness of washing. Roy et al. [13] conducted trials with 99 patients randomized to washing with soap and water or no washing, and found a significantly higher incidence of moist desquamation in the non-washing group; while Campell et al. [11] randomized 99 women receiving adjuvant radiotherapy for breast cancer into one of three groups with different washing practices, and found a significant reduction in itching score at the end of treatment and a reduction in erythema and desquamation scores at 6 or 8 weeks after treatment in patients who washed with soap and water independent of bolus dose.

Based on these results, we established Step 1 in our DeCoP as washing only.

Patients received elaborate instructions on how to wash properly. The median time to the onset of grade 2 dermatitis was 43.5 days (range 23–60 days). The frequency of Steps 2 or 3 at 2 weeks and 1 month after the end of radiotherapy was 19 and 2%, respectively. These results show that radiation dermatitis in head and neck lesions can be managed with minimal intervention.

This report has two major limitations. One is that, in our trial, we could not mention the prevention of dermatitis. Another is that it is not enough to mention whether corticosteroids are useful or not for the management of dermatitis because this trial is not a randomized study.

Given this minimal invasiveness, the DeCoP used here appears to be not only useful for clinical practice, but also effective as a control measure for large-scale randomized control trials investigating topical corticosteroids and other medications for dermatitis. Such studies are necessary because although corticosteroids remain frequently prescribed for the management of radiation dermatitis in clinical practice, the evidence for their effectiveness has been inconclusive [9, 12, 14–16].

To change our clinical practice, a further large-scale and qualified phase III study may play a great role.

In conclusion, the results above suggest that radiation dermatitis in head and neck lesions may be manageable if only gentle washing and moistening of the wound-healing environment is done during radiotherapy.

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Conflict of interest There is no conflict of interest.

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