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Phase I trial of chemoradiotherapy with the combination of S-1 plus cisplatin for patients with unresectable locally advanced squamous cell carcinoma of the head and neck

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The aim of the present study was to determine the maximum tolerated dose (MTD) of S-1 in combination with chemoradiotherapy (CRT) in patients with unresectable locally advanced squamous cell carcinoma of the head and neck, and evaluate the difference in pharmacokinetics of S-1 when administered as a suspension via a feeding tube or orally as a capsule. Chemotherapy consisted of administration of S-1 twice daily on days 1–14 at escalating doses of 40, 60 and 80 mg/m^2 per day, and cisplatin at 20 mg/m^2 per day on days 8–11, repeated twice at a 5-week interval. Single daily radiation of 70 Gy in 35 fractions was given concurrently starting on day 1. Two additional cycles of chemotherapy were planned after the completion of CRT. Before starting CRT, each patient received S-1 via two different administration methods. Twenty-two patients were enrolled. The MTD was reached with S-1 at 80 mg/m^2 per day, with two of six patients experiencing febrile neutropenia lasting more than 4 days. All four patients whose creatinine clearance was decreased to <60 mL/min after the first cycle of chemotherapy developed febrile neutropenia lasting more than 4 days. Pharmacokinetic analysis revealed that the 5-fluorouracil area under the curve did not significantly differ by the administration route. S-1 at 60 mg/m^2 per day for 14 days was well tolerated with concurrent CRT. Administration of S-1 as a suspension or by whole capsule can be considered therapeutically interchangeable. Although these data are preliminary, activity was highly promising, and this approach warrants further investigation. (*Cancer Sci*, doi: 10.1111/j.1349-7006.2010.01799.x, 2010)

Head and necks cancers are the sixth most common cancer in the world, and approximately 500 000 new cases are projected annually.[1] An estimated 60% of these patients will present with locally advanced disease (stage III/IV).

In the last 20 years, the integration of concurrent chemoradiotherapy (CRT) has advanced the treatment of locoregionally advanced squamous cell carcinoma of the head and neck (SCCHN), improving locoregional control and overall survival (OS) compared with radiotherapy (RT) alone while allowing organ preservation. However, half of these cases will recur, indicating a clear need for further therapeutic intervention. Moreover, although ample data provide a high level of evidence for the benefit of platinum-based CRT for unresectable locally advanced SCCHN,[2] an optimal CRT regimen is yet to be defined.

S-1 is a novel oral fluoropyrimidine derivative that consists of tegafur, 5-chloro-2, 4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) at a molar ratio of 1:0.4:1. Tegafur is a prodrug of 5-fluorouracil (5-FU).[3] CDHP augments the activity of 5-FU by inhibiting dihydropyrimidine dehydrogenase (DPD). Oxo reduces gastrointestinal (GI) toxicity by inhibiting orotate phosphoribosyl transferase and 5-FU phosphorylation in intestinal mucosa.

S-1 has been shown to be active against head and neck cancer, producing a response rate of 34%.[4] The combination of cisplatin (CDDP) and S-1 shows promising activity (response rate 67.6%) with acceptable toxicity for locally advanced head and neck cancer.[5] The combination of S-1 and fractionated radiotherapy is more effective against human oral cancer xenografts than either modality alone.[6]

A previous study demonstrated that the combination of S-1 and fractionated radiotherapy was more effective against human oral cancer xenografts than either treatment alone,[6] while another demonstrated that S-1 had a greater effect on radiosensitivity in human non-small-cell lung cancer xenografts in mice than uracil/tegafur (UFT), which also is an oral fluoropyrimidine derivative but does not contain CDHP.[7,8] CDHP enhanced radiosensitivity in human lung cancer cells in a dose escalation-dependent manner, suggesting that S-1 might be a more powerful enhancer of radiosensitivity in cancer than 5-FU or UFT.

Against this, however, no study has reported the feasibility and safety of S-1 in combination with CRT in patients with locally advanced SCCHN. We therefore conducted a single institutional, phase I, dose-escalation study of S-1 in combination with CRT in patients with unresectable locally advanced SCCHN.

Because CRT not only improves locoregional control but also exacerbates toxicities such as mucositis and dysphagia, patients may have difficulty in swallowing capsules. S-1 should therefore be administered as a suspension via a feeding tube. To date, however, no adequate bioavailability data for S-1 when administered as a suspension via a feeding tube has been available. For this reason, we also evaluated the difference in pharmacokinetics of S-1 when administered as a suspension via a feeding tube or orally by capsule.

Patients and Methods

Eligibility. Eligibility for the present study required a histologically or cytologically confirmed diagnosis of SCCHN with unresectable locally advanced disease, including postoperative local recurrence. Careful evaluation for unresectability was required from a multidisciplinary conference, which included head and neck surgeons, radiation oncologists and medical

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oncologists. Criteria for unresectability were carefully defined as follows: (i) technical unresectability, considered to mean tumors fixed to the carotid artery, mastoid, base of the skull or cervical spine; and (ii) physician determination of low surgical curability based on neck lymph node metastases such as N2c-3. Medical unsuitability for resection was not sufficient for patient eligibility; eligibility also required an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, age 20–75 years and adequate organ function. Written informed consent was required from all patients before the start of any therapy.

Patients were excluded if they had any of the following conditions: previous chemotherapy or radiotherapy; concurrent active malignancy except excised intramucosal gastric or esophageal cancer that could be removed by endoscopic mucosal resection; pharyngeal fistula; active bleeding from the GI tract; active infection; serious medical problem that might interfere with the achievement of study objectives; pregnancy or lactation; or expected survival <3 months.

Treatment. Baseline evaluation included patient history, physical examination, panendoscopy, dental evaluation, head and neck magnetic resonance imaging (MRI), computed tomography (CT) scan of the chest and abdomen, routine laboratory studies and electrocardiography (EKG). The treatment schedule is shown in Fig. 1.

Radiotherapy was done with 70 Gy/35 fractions over 7 weeks using six mega volt (MV) X-ray and 3-D radiotherapy techniques, and was started on day 1. Intensity-modulated radiotherapy was unavailable during this study. Gross tumor volume (GTV) was determined based on endoscopic or radiographic findings. Clinical target volume (CTV) was defined by adding 0.5 to 1 cm to the GTV. Planning target volume (PTV) was determined by adding appropriate margins to the CTV with consideration for physiological organ motion and daily set-up error. All patients underwent prophylactic nodal irradiations encompassing bilateral upper, middle and lower jugular, accessory and retropharyngeal lymph nodes up to 40–46 Gy. An additional 24–30 Gy was added to the PTV. Maximum dose to the spinal cord was restricted to 46 Gy, and posterior neck node was boosted using a 9–12 MeV electron beam as indicated. The radiotherapy dose was prescribed to the midplane along the beam axis, and dose deviation within the PTV was restricted to ±5% of the prescribed dose.

Chemotherapy consisted of administration of S-1 twice daily on days 1–14 at escalating doses of 40, 60 and 80 mg/m^2 per day, and 2-h infusion of CDDP at 20 mg/m^2 per day on days 8–11, repeated twice with a 5-week interval. Hydration consisted of 1 L of normal saline solution over 2 h prior to CDDP, as well as mannitol 12.5 gm by i.v. bolus infusion and 2 L of normal saline solution over 4 h following CDDP administration. Two additional cycles of S-1 and CDDP at the same dose level of CRT, repeated with a 4-week interval, were planned 4 weeks after the completion of CRT. Neutrocytes had to have recovered to at least 2000 cells/mm^3 and grade 1 creatinine or >50 mL/min of creatinine clearance was required by the time of the next cycle.

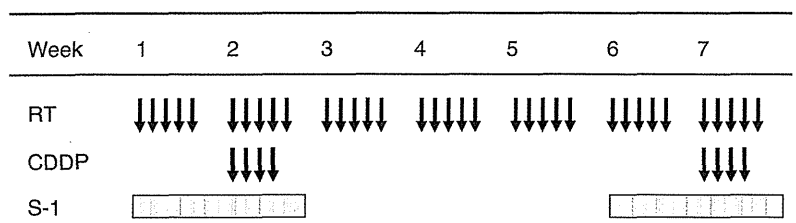
All patients underwent emplacement of a percutaneous endoscopic gastrostomy (PEG) feeding tube prior to the initiation of treatment. Prophylactic use of granulocyte-colony stimulating factor was not permitted. Additional treatment was not permitted unless persistent disease or disease progression was observed. When a patient had persistent or recurrent disease at the completion of CRT, surgical salvage was considered.

Toxicity. Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 2.0. Any of the following adverse events observed within 30 days after the completion of CRT was deemed a dose-limiting toxicity (DLT): (i) febrile neutropenia lasting more than 4 days; (ii) grade 4 thrombocytopenia; (iii) grade 3 or 4 non-hematological toxicities except grade 3 anorexia, nausea, vomiting, stomatitis, esophagitis, infection due to stomatitis, dysphagia and skin toxicity; (iv) cessation of treatment due to an adverse event; or (v) treatment-related death. The maximum-tolerated dose (MTD) was defined as the dose at which more than two of six patients experienced a DLT. The recommended safe dose for further study was assessed at the dose level immediately below the MTD.

A minimum of three assessable patients was treated at each dose level. If one of the three patients at a given dose experienced a DLT, three more patients were accrued at the same dose level. If more than two of six patients at a given dose experienced a DLT, three more patients were treated at the next lower dose level. If less than one of six patients experienced a DLT, an additional six patients were accrued at the same dose level to determine the recommended dose.

Sample collection. Before the initiation of CRT, patients who gave consent underwent pharmacokinetic investigation. A single dose of S-1 as a capsule formulation was administrated orally 4 days before the start of CRT (day -4), while the same dose was given through a feeding tube as a suspension 2 days before the start of CRT (day -2). Suspensions were prepared by simple dissolution of a S-1 capsule in hot water. Peripheral blood samples were drawn before and at 0.5, 1, 2, 4, 6, 8, 10 and 24 h after each administration. Heparinized blood was centrifuged at 3000 rpm for 15 min at 4°C, and plasma was stored at −80°C.

Pharmacokinetic analysis. Tegafur, 5-FU, CDHP and Oxo were analyzed according to the method of Matsushima *et al.*[9] Pharmacokinetic parameters of Tegafur, 5-FU, CDHP and Oxo were estimated according to a standard noncompartmental method. Maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}) were taken from the observed data. The area under the plasma-concentration time curve (AUC) for time 0 to infinity was estimated by summing AUC from 0 to time t (AUC_{0-t}) and C_{tlast}/k, where C_{tlast} was the concentration at the last measured point. The apparent rate constant of elimination (k) was estimated by linear regression on the logarithm of the plasma



RT: 2 Gy/Fr x 33 or 35 Fr (total 70 Gy)
CDDP: 20 mg/m²/day, iv, days 8–11, days 43–46
S-1: 40, 60, 80 mg/m²/day, twice daily po, days 1–14, days 36–49

Fig. 1. Treatment schedule. Two additional cycles of S-1 and cisplatin (CDDP) at the same dose level of the chemoradiotherapy (CRT), repeated at a 4-week interval, were planned 4 weeks after the completion of the CRT. RT, radiotherapy.

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concentrations versus time, and AUC_{0-t} was estimated using the log trapezoidal method.

Criteria for response. Tumor responses were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) by panendoscopy, MRI of the head and neck and CT scan of the chest and abdomen.

End-points and statistical methods. The primary end-point in the present study was the MTD and DLT of S-1 in combination with a fixed dose of CDDP and RT. Safety and feasibility of this treatment were evaluated in patients with unresectable locally advanced SCCHN. Secondary end-points included complete response rate, progression-free survival (PFS), locoregional PFS, overall survival (OS) and pharmacokinetics of S-1 when administered as a suspension via the feeding tube.

The survival curve was estimated using the Kaplan–Meier method. Safety and efficacy analyses were both conducted on an intention-to-treat (ITT) population, defined as all patients enrolled in the study who received at least one dose of RT. A subject's PFS was defined as the time from the date of the first administration of CRT to the first documentation of disease progression, subsequent therapy or death. The OS was determined from the date of the first administration of CRT to the date of death or the last confirmed date of survival. Locoregional PFS was defined as the time from the date of the first administration of CRT to the first documentation of locoregional disease progression. Statistical data were obtained using the SPSS software package (SPSS 11.0 Inc., Chicago, IL, USA).

This study was conducted at the National Cancer Center Hospital East. The protocol was approved by the Institutional Review Board at the National Cancer Center.

Results

Patient and disease characteristics. Twenty-two patients were enrolled between February 2003 and January 2005. One patient did not receive CRT because it made the performance status worse due to disease progression, leaving 21 patients in the ITT population. Patient characteristics in the ITT population are listed in Table 1. The most common site of the primary lesion was the hypopharynx (59%). One patient had unresectable local recurrence after total larnyngectomy for hypopharyngeal cancer and the other 20 had never received any prior treatment for head and neck cancer.

Treatment administration. A total of 69 cycles of chemotherapy was administered. The number of cycles was two in seven patients, three in three patients, four in 10 patients and six in one patient. The reasons for the administration of less than four cycles were toxicities ($n = 2$), physician decision due to concern about tolerance ($n = 2$) and patient refusal due to achievement of complete remission ($n = 6$). One patient received six cycles due to persistent disease that could not be removed by salvage surgery.

Three patients were treated at the dose level of S-1 40 mg/m^2 without DLT. Of the first three patients who received S-1 at the 60 mg/m^2 dose level, one patient blacked out after straining at stool due to constipation on day 16 and developed grade 3 ischemic colitis, but reported recovery within 1 week under conservative treatment including hydration. Because he finished taking S-1 on day 14 and did not develop any GI toxicity including mucositis or diarrhea before suffering from this colitis, the safety committee decided that this colitis was not likely related to the study treatment. Two other patients had no DLT and dose escalation subsequently proceeded. Of the first three patients treated at a dose level of S-1 80 mg/m^2, one developed febrile neutropenia lasting more than 4 days, leading to the accrual of an additional three patients at this level. Thus, six patients were treated at the dose level of S-1 80 mg/m^2, of whom two developed febrile neutropenia lasting more than 4 days. The MTD was therefore set at 80 mg/m^2 per day of S-1.

Table 1. Patients' characteristics

Characteristic	No. patients ($n = 21$)
Age (years)	
Median	62
Range	45–73
Sex	
Male	19
Female	2
ECOG performance score	
0	15
1	6
Site of primary tumor	
Hypopharynx	13
Pharynx	1
Oropharynx	5
Nasopharynx	2
AJCC stage	
IV	20
Local relapse	1
T stage	
T1	4
T2	5
T3	3
T4	8
Local relapse	1
N stage	
N0	3
N2a	1
N2b	2
N2c	6
N3	8

AJCC, American Joint Committee on Cancer.

Three additional patients were treated at the dose level of S-1 60 mg/m^2, one of whom experienced grade 3 diarrhea with grade 3 infection. To determine the recommended dose of S-1, six additional patients (total of 12 patients) were treated at the dose level of S-1 60 mg/m^2, three of whom developed febrile neutropenia lasting for more than 4 days. One of them experienced febrile neutropenia lasting for 2 weeks despite using granulocyte colony-stimulating factor supports and the diagnosis of myelodysplastic syndrome was made by bone marrow study. One week after the completion of CRT, another of these three patients who experienced febrile neutropenia developed grade 3 diarrhea, which occurred 1 day after the development of febrile neutropenia. Because the administration of S-1 had finished 1 week previously, this diarrhea was not related to S-1 but to the neutropenia or antibiotic drugs, and was not regarded as a DLT.

During CRT, eight patients (38%) received administration of S-1 via a feeding tube, and a total of 14% of the planned doses of S-1 were administered via a feeding tube during CRT. The number of patients who received S-1 via a feeding tube at each dose level was one of three at 40 mg/m^2, four of 12 at 60 mg/m^2 and three of six at 80 mg/m^2.

All patients were treated with conventional 3-D RT and received planned doses of CDDP. One patient received a total of 68 Gy while the other 20 received 70 Gy. Four patients required the splitting of RT due to adverse events, including colitis in one patient, grade 3 dermatitis and infection in one patient and neutropenia in two patients. Of the two patients who developed neutropenia, one was treated at the dose level of S-1 80 mg/m^2, while the second was treated at 60 mg/m^2.

Toxicity. Overall toxicities during treatment are listed in Table 2. Grade 3 or 4 toxicities by the S-1 dose level are listed in Table 3. The incidence of grade 3 or 4 neutropenia and febrile neutropenia increased with increasing dose, with half of those

treated at 80 mg/m^2 experiencing febrile neutropenia. All four patients whose creatinine clearance was decreased to <60 mL/min after the first cycle of chemotherapy developed febrile neutropenia lasting more than 4 days. Of these, two each were treated at S-1 dose levels of 60 and 80 mg/m^2.

The incidence of grade 3 or 4 mucositis and dysphagia increased with increasing dose and occurred in all patients treated at 80 mg/m^2, indicating that S-1 at 80 mg/m^2 was intolerable in this treatment. One patient who achieved a complete response after completion of CRT experienced pharyngeal stricture as an adverse event, declined surgical treatment and is still alive without any evidence of recurrence. Fifteen patients (71%) received nutritional support via a feeding tube, with a median feeding tube duration of 199 days and 1-year feeding tube dependence of 14%.

Table 2. Overall toxicity (*n* = 21)

Toxicity	No. patients (Grade)				% of patients	
	1	2	3	4	Grade 1–2	Grade 3–4
Hematological toxicity						
Leucopenia	8	4	3	5	57	38
Neutropenia	5	2	3	5	33	38
Febrile neutropenia	–	–	6	0	–	29
Anemia	10	6	3	2	76	24
Thrombocytopenia	10	2	2	1	57	14
Non-hematological toxicity						
Nausea	4	4	5	0	38	24
Vomiting	8	2	0	0	48	0
Anorexia	4	3	1	0	33	5
Fatigue	5	6	1	0	52	5
Mucositis	4	1	14	1	24	71
Dysphagia	3	1	15	0	19	71
Dermatitis	3	12	3	0	71	14
Diarrhea	1	2	2	0	14	10
Elevated bilirubin	2	1	0	0	14	0
Elevated AST	2	4	0	0	29	0
Elevated ALT	3	4	0	0	33	0
Elevated creatinine	2	1	0	0	14	0
Xerostomia	7	12	0	0	90	0
Salivary change	3	9	0	0	57	0

ALT, alanine transaminase; AST, aspartate transaminase.

Table 3. Grade 3 or 4 toxicity by S-1 dose level

	Grade 3 or 4 toxicity					
	S-1 dose level: 40 mg/m^2 per day (*n* = 3)		S-1 dose level: 60 mg/m^2 per day (*n* = 12)		S-1 dose level: 80 mg/m^2 per day (*n* = 6)	
	No. patients	%	No. patients	%	No. patients	%
Hematological toxicity						
Leucopenia	1	33	5	42	2	33
Neutropenia	1	33	4	33	3	50
Febrile neutropenia	0	0	3	25	3	50
Anemia	0	0	4	33	1	17
Thrombocytopenia	0	0	2	17	1	17
Non-hematological toxicity						
Anorexia	0	0	3	25	2	33
Mucositis	1	33	7	58	6	100
Dysphagia	1	33	8	67	6	100
Dermatitis	0	17	2	17	1	17
Diarrhea	0	1	2	17	0	0

Pharmacokinetic analysis of S-1. Pharmacokinetic data on administration of S-1 as oral capsules (day -4) and suspensions via a feeding tube (day -2) were available for 16 patients (Table 4). Tmax values for tegafur, 5-FU, CDHP and Oxo were significantly lower with the suspension than oral capsules, while Cmax values for tegafur, CDHP and Oxo were significantly higher. However, the Cmax for 5-FU and AUC of all parameters did not significantly differ by administration route. Moreover, although no clear relationship was seen between any parameter and adverse events, a weak correlation was seen between the AUC of tegafur and the rate of neutropenia ($P = 0.106$).

Treatment outcomes. Of the 21 patients treated with CRT, 18 experienced a complete response. Two additional patients who had been diagnosed with residual neck lymph node metastasis underwent salvage neck dissection, and pathology revealed no residual tumor. With a median follow up of 49 months (range,

Table 4. Phamacokinetics of S-1 by the administration route (*n* = 15)

	Administration route			
	Oral (*n* = 15)	Feeding tube (*n* = 15)	Ratio	*P*-value
Tegafur				
T_{max} (min)				
Median	126.0	65.0	0.50	0.0012
Range	30–483	28–246	0.13–1.03	
C_{max} (ng/mL)				
Median	1571.0	1841.1	1.11	0.0009
Range	729–2373	804–2658	0.95–1.49	
AUC (μg × min/mL)				
Median	1416.6	1421.8	0.99	0.64
Range	573.2–3888.1	408.1–4306.5	0.71–1.16	
5-FU				
T_{max} (min)				
Median	239.0	121	0.78	0.013
Range	60–483	59–246	0.26–2.00	
C_{max} (ng/mL)				
Median	120.1	107.4	1.00	0.56
Range	26.5–188.6	29.4–176.5	0.73–1.47	
AUC (μg × min/mL)				
Median	33.6	29.4	0.94	0.63
Range	12.5–54.2	16.8–48.7	0.64–1.34	
CDHP				
T_{max} (min)				
Median	120.0	62	0.50	0.0009
Range	60–483	30–246	0.12–1.03	
C_{max} (ng/mL)				
Median	183.8	205.2	1.22	0.04
Range	72.0–358.8	101.5–584.6	0.71–1.78	
AUC (μg × min/mL)				
Median	66.0	65.7	1.03	0.15
Range	28.6–83.3	37.9–115.0	0.83–1.42	
Oxo				
T_{max} (min)				
Median	120.0	118.0	0.51	0.0005
Range	90–243	58–122	0.26–1.01	
C_{max} (ng/mL)				
Median	26.2	35.0	1.51	0.041
Range	3.8–60.1	11.5–212.4	0.48–3.58	
AUC (μg × min/mL)				
Median	7.5	9.2	1.39	0.21
Range	1.9–18.7	3.1–57.9	0.68–4.71	

5-FU, 5-fluorouracil; CDHP, 5-chloro-2,4-dihydroxypyridine; Oxo, potassium oxonate.

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44–62 months), local recurrence only, distant metastasis and both local recurrence and distant metastasis were observed in four, four and one patient, respectively. A total of nine patients died, five from local recurrence, three from disease progression of distant metastases and one from progression of residual neck lymph node. Estimated rates of 3-year locoregional PFS, PFS and OS were 75%, 48% and 62% respectively.

Discussion

In this phase I study of S-1 in combination with CRT in patients with unresectable locally advanced SCCHN, MTD of S-1 was 80 mg/m^2 per day. S-1 at 60 mg/m^2 per day for 14 days with concurrent CRT was well tolerated, and provided promising activity in these patients. Administration of S-1 as a suspension via a feeding tube or by oral capsule can be considered therapeutically interchangeable.

S-1 contains CDHP, which inhibits DPD. As 50% of CDHP is excreted in the urine, renal dysfunction might directly affect the inhibitory effect on DPD and lead to increased 5-FU concentrations.[10] Although the current standard dosing regimen for cisplatin is a single intravenous infusion of 100 mg/m^2, this regimen has a higher incidence of renal toxicities than lower doses. We therefore selected divided doses of the CDDP to reduce renal toxicity.

The incidence and severity of both hematological and non-hematological toxicities increased in accordance with the increasing dose. At a dose level of S-1 80 mg/m^2, half experienced febrile neutropenia lasting more than 4 days and all developed grade 3 or 4 mucositis, indicating that the dose of S-1 80 mg/m^2 was intolerable. The MTD was therefore set at 80 mg/m^2 per day of S-1. Two patients treated with S-1 at 60 mg/m^2 experienced grade 3 diarrhea. One of these patients did not receive anti-diarrhea drugs until the development of grade 3 diarrhea and infection, which was regarded as a DLT. The second experienced grade 3 diarrhea following grade 3 febrile neutropenia. Because the administration of S-1 had finished 1 week previously, this diarrhea was not related to S-1 but to the neutropenia or antibiotic drugs, and was not regarded as a DLT. However, this patient experienced grade 3 febrile neutropenia for more than 4 days, which was regarded as a DLT. Three patients experienced grade 3 febrile neutropenia for more than 4 days at S-1 60 mg/m^2. In other words, four of 12 patients receiving S-1 at 60 mg/m^2 experienced a DLT. Another experienced febrile neutropenia lasting 2 weeks despite the use of granulocyte colony-stimulating factor and was subsequently diagnosed with myelodysplastic syndrome on bone marrow study, indicating that this patient was inappropriate for evaluation of the recommended dose of S-1 in combination with CRT.

In the present study, all four patients whose creatinine clearance was decreased to <60 mL/min after the first cycle of chemotherapy developed febrile neutropenia lasting more than 4 days, and two of these were treated at a dose level of S-1 60 mg/m^2. The higher incidence of febrile neutropenia in the present study is therefore likely related to decreased creatinine clearance. Grade 1 creatinine or creatinine clearance of more than 50 mL/min had to have occurred by the time of the next cycle, while dose modification according to creatinine clearance was not performed. Dose modification according to creatinine clearance could have reduced or prevented these toxicities. Based on these results, we are convinced of the need for dose modification according to creatinine clearance in the treatment with S-1. In this regard, recent studies of S-1 have indeed used dose modification according to creatinine clearance.[11,12]

Although a slightly higher incidence of DLT was observed at this level, suggesting that it was not suitable for consideration as the recommended dose (RD), these toxicities might have been reduced by dose modification according to creatinine clearance and appropriate anti-diarrhea medication. Furthermore, this dose level was well tolerated in the other eight patients, with acceptable toxicity. We therefore established S-1 at 60 mg/m^2 per day as the RD. The clinically appropriate dose of S-1 in combination with CRT can only be determined in phase II trials.

Previous studies demonstrated a significant correlation between 5-FU plasma concentration, in particular 5-FU AUC, and therapeutic activity and toxicity.[13–17] Moreover, two phase I studies of S-1 showed a significant correlation between diarrhea grade and 5-FU AUC,[17,18] one of which additionally demonstrated a significant correlation between diarrhea grade and 5-FU Cmax.[18]

In the present study, pharmacokinetic analysis revealed that the Tmax of all parameters, including tegafur, 5-FU, CDHP and Oxo, were significantly lower on administration as a suspension, whereas the Cmax of tegafur, CDHP and Oxo were significantly higher than with oral capsules, indicating that the absorption of S-1 is higher in suspension. However, the Cmax for 5-FU and AUC of all parameters did not significantly differ by the administration route, indicating that the two routes can be considered therapeutically interchangeable.

In the present study, 18 of 21 patients achieved a complete response, while an additional two patients who had been pathologically diagnosed revealed no residual tumor on salvage neck dissection, with 3 years OS of 61.9%. Considering the small number of patients, these findings indicate that this regimen may provide promising activity in patients with unresectable locally advanced SCCHN.

Severe mucositis in locally advanced SCCHN patients receiving CRT frequently leads to dysphasia and weight loss. These patients may require adequate nutritional support to avoid treatment interruption, which can adversely impact the treatment outcome. However, although the relative benefits of prophylactic versus therapeutic PEG feeding tube placement are controversial, we are convinced that prophylactic PEG feeding tube replacement is indispensable to the completion of these high-intensity treatments. Although all PEG feeding tube replacements in this study were performed by pull techniques, few severe complications and no tumor seeding were observed. Furthermore, despite the high incidence of toxicities, all but one patient completed the CRT, indicating the likely usefulness of a prophylactic PEG feeding tube.

Feeding tube placement prior to CRT due to pre-existing dysphagia and advanced T stage are associated with prolonged feeding tube dependence.[19] In the present study, 71% of patients received nutritional support via a feeding tube, with a median feeding tube duration of 199 days and a 1-year feeding tube dependence of 14%. Additionally, one patient who achieved a complete remission subsequently experienced pharyngeal stricture after the completion of CRT, indicating that all patients should receive evaluation by a speech-language pathologist throughout the course of CRT, swallowing exercises, even though a feeding tube is in place, and rapid rehabilitation.

Concern has been expressed over the considerable ethnic differences in the tolerated doses of S-1. These relate to the varying efficiency rates of conversion of tegafur to 5-FU by CYP2A6 of the CYP450 enzyme system, now identified as the principal enzyme responsible for this conversion process.[20–23] A phase I study of S-1 plus CDDP in Western patients with advanced gastric carcinoma showed that the S-1 dose tolerated by Western patients is lower than that by Japanese patients, but that the AUC of FU appears higher in white rather than Japanese patients in a comparable dose range of S-1.[24] This is mostly attributed to different polymorphisms in the *CYP2A6* gene among Asians and whites. The RD of the present study is likely to be unsuitable for Western patients, and further study

to determine the RD of this combination for these patients is required.

In conclusion, S-1 at 60 mg/m^2 per day for 14 days was well tolerated with concurrent CRT with CDDP. Furthermore, no difference was seen in the pharmacokinetics of S-1 between administration as a suspension and orally as a whole capsule, indicating that these can be considered therapeutically interchangeable. Although these data are preliminary, activity was highly promising, and this approach warrants further investigation. A multicenter phase II study of this approach by the Japan Clinical Oncology Group (JCOG) is ongoing.[11]

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Disclosure Statement

The authors have no conflict of interest.

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ORIGINAL ARTICLE

PROSPECTIVE TRIAL OF CHEMOTHERAPY-ENHANCED ACCELERATED RADIOTHERAPY FOR LARYNX PRESERVATION IN PATIENTS WITH INTERMEDIATE-VOLUME HYPOPHARYNGEAL CANCER

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Abstract: *Background.* Altered fractionation radiotherapy (RT) improves locoregional control in head and neck cancer without aggravation of late adverse events. To improve successful larynx-preservation rates in patients with resectable, intermediate-volume hypopharyngeal cancer, a prospective trial of chemotherapy-enhanced accelerated RT was conducted.

Methods. Patients with T2 to T4 hypopharyngeal cancer received 40 Gray (Gy)/4 weeks to the entire neck followed by boost RT administering 30 Gy/2 weeks (1.5 Gy twice-daily fractionation). Cisplatin and 5-fluorouracil were administered concomitantly only during boost RT.

Results. Thirty-five patients were enrolled in this study. All patients completed this protocol as planned. After a median follow-up period for surviving patients of 59 months (24–90 months), overall survival and local control rates at 3 years were 91% (95% confidence interval, 81% to 100%), and 88% (79% to 99%), respectively. All surviving patients maintained normalcy of diets.

Conclusion. This regimen was feasible with encouraging oncological and functional outcomes. © 2011 Wiley Periodicals, Inc. *Head Neck* **00:** 000–000, 2011

Keywords: hypopharyngeal cancer; accelerated fractionation radiotherapy; chemotherapy; larynx preservation; long-term swallowing function

Approximately one fourth of oral cavity or pharyngeal cancers in Japan originate from the hypopharynx, and the estimated incidence of patients with hypopharyngeal cancer is about 2500 per year.[1,2] Larynx-preserving approaches for hypopharyngeal cancer showed no obvious difference in overall survival compared to other surgical approaches in a randomized study[3] as well as in a large population-based study.[4] Conventional fractionation radiotherapy (RT) alone for patients with early-stage hypopharyngeal cancer with T2 disease achieved a local control rate of approximately 60%.[5,6] RT alone using altered fractionation significantly improved local control rates without deterioration of serious late adverse events.[7,8] This approach could achieve favorable larynx-preservation rates in selected patients with hypopharyngeal cancer with low-volume, T1 or T2 primary tumors which had tumor volumes of 7 mL or smaller.[9,10] However, less favorable results were expected for other patients with larger hypopharyngeal cancers that required total laryngectomy.[10,11] Therefore, the combination of chemotherapy with RT is required to improve larynx-preservation rates in these patients.[12]

Because hypopharyngeal cancer originates from the narrowest part of the upper digestive tract, late dysphagia and aspiration due to consequential late effects are not uncommon even after successful eradication of the disease after intensive chemoradiotherapy (CRT).[13–16] Therefore, special attention should be paid to minimize severity and duration of serious mucosal toxicity by a deliberate combination of altered fractionation RT and/or chemotherapy with meticulous patient selection according to the morphology and volume of the primary tumor.[10,17]

High incidence of distant metastasis in patients with hypopharyngeal cancer was mainly because of the high frequency of advanced nodal disease at the time of initial presentation.[18] If a patient has an intermediate-volume tumor without advanced nodal metastasis, tumor control above the clavicle instead of prevention of systemic tumor dissemination should be prioritized. We previously reported a favorable local cure rate after conventional fractionation RT in patients with intermediate-volume disease at the pharyngolarynx; however, further improvement of

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local control with good function is needed.[19] This study was based on the principle that use of chemotherapy as a radiation sensitizer should not compromise the benefit of altered fractionation RT alone in terms of long-term swallowing function in these patients.[7,8] Accelerated fractionation that delivers dose-dense RT during the latter part of the entire treatment is a reasonable strategy to overcome accelerated repopulation of the tumor, which is supposed to begin at approximately 4 weeks after commencement of RT.[8,20,21] The aim was to enhance the effect of treatment using both twice-daily RT and chemotherapy only during the period when acceleration of tumor repopulation is to be expected. Although the incidence of these patients was expected to be limited, and the true efficacy should be tested in multiinstitutional collaborative studies, preliminary results of this "chemotherapy-enhanced" accelerated fractionation RT were promising.[22] Therefore, matured results of a prospective, single institutional trial were reported here to demonstrate the safety and validity of conducting a larger trial of this regimen.

MATERIALS AND METHODS

Patient Population. Patients were required to have previously untreated, histologically proven squamous cell carcinoma of the hypopharynx that was judged amenable to margin-free resection with total laryngopharyngectomy and neck dissection by expert head and neck surgeons in our institution. Those who were considered as candidates for partial laryngectomy or who had T1 disease were ineligible for this study. In addition, the following eligibility criterion were required: age ranging from 20 to 75 years; no bilateral lymph node metastasis on CT and/or MRI scans; no evidence of distant organ metastasis (clinically M0); Zubrod Performance Status (PS) of 0 to 2; no history of RT for the head and neck area; adequate bone marrow and organ function; no history of other malignancies within 5 years before enrollment; and no history of ischemic heart disease and/or symptomatic cerebrovascular accident within 3 months before enrollment. Patients who had simultaneous superficial esophageal and/or gastric cancers that were judged amenable to margin-free resection using endoscopic mucosal resections were eligible for the study. All patients provided written informed consent. We received approval for this study from our institutional ethics committee.

Pretreatment Evaluation. Disease was staged according to the American Joint Committee on Cancer Staging Manual (6th edition). Staging procedures consisted of physical examination, head and neck fiberscope, CT and/or MRI of the head and neck region, chest X-ray, upper abdominal ultrasound, and gastroesophageal endoscopy. CT of the chest and bone scans were performed as indicated. Laboratory studies included a complete blood cell count, routine liver and kidney function tests, and electrocardiography. All patients underwent pretreatment dental examinations, and dental therapy was done as indicated before the start of RT. Nutritional support by using a nasogastric tube or percutaneous gastrostomy was not done in this protocol.

Radiotherapy. A total dose of 40 Gray (Gy)/4 weeks using 2 Gy once-daily fractionation was administered to the primary tumor, bilateral level II to IV lymph node stations, and retropharyngeal lymph nodes according to the American Joint Committee on Cancer Staging Manual (6th edition). This was followed by boost RT administering 30 Gy/2 weeks (1.5 Gy twice-daily fractionation) to the primary tumor with 2-cm margins. Interfraction interval was set as $\geq$6 hours. Maximum efforts were taken, if appropriate, to exclude the base of tongue and cervical esophagus at >2 cm below the caudal edge of the cricoid cartilage from irradiated volume of the boost RT. If a patient had gross nodal disease extending above the posterior belly of the subdigastric muscle and/or to level IV, which necessitated a larger irradiated volume than that described above during boost RT, neck dissection was performed before the start of RT. This was followed by a total of 55 Gy of RT that was administered to the surgical bed of this up-front nodal dissection, followed by additional 15 Gy to the primary tumor. Maximum dose to the spinal cord was restricted to 46 Gy/24 fractions. RT was delivered using 6 MV X-rays in all patients with 3-dimensional RT planning. Intensity-modulated radiotherapy was not used in this group of patients.

Chemotherapy. A single course of chemotherapy was concomitantly administered during the boost RT in expectation of a radiosensitizing effect.[23,24] Cisplatin 80 mg/m^2 was administered with intravenous hydration on the first day of chemotherapy, and 4-day continuous infusion of 5-fluorouracil 400 mg/m^2/day was started on the same day. Patients were hospitalized during the course of chemotherapy and received hydration and antiemetic therapy as indicated.

Dose Modifications. Grade 4 hematological toxicity or grade $\geq$3 dysphagia and/or swallowing pain required treatment break until these toxicities became grade $\leq$2. Chemotherapy was started only when the following criterion were fulfilled: white blood cell count $\geq$2000/mm^3, hemoglobin level $\geq$8.0 g/dL, platelet count $\geq$100,000/mm^3, any gastrointestinal toxicities of less than grade 3, serum bilirubin level $\leq$1.5 mg/dL, serum creatinine level $\leq$1.5 mg/dL, and dermal toxicity of less than grade 2. If patients did not meet these criterion, chemotherapy was postponed without RT break and administered only when patients satisfied the criterion within 7 days.

Outcome Measures and Statistical Considerations. Low accrual rate was expected in a single institutional setting, and experience of administering altered fractionation RT for hypopharyngeal cancer was limited in Japan at the time of protocol development.[6] Therefore, this trial was conducted as a feasibility study to plan a multiinstitutional trial of this regimen to evaluate the true efficacy with a sufficient number of patients. The primary endpoint was completeness of the protocol treatment without unplanned treatment break or dose modification. This trial used a 2-stage design wherein the expected rate of completeness was defined as 80%. This was tested against the threshold rate of 60% or lower with an alpha level of 5% and a power of 80%, which required an initial enrollment of 13 patients. If <8 of these 13 patients completed the protocol without unplanned break and dose modifications, the trial would be stopped. Otherwise, enrollment would be extended to 35 patients and the rate of completeness determined. Secondary endpoints were local control rate, progression-free survival, overall survival, and adverse events. Follow-up visits were requested monthly within 2 years after completion of RT, at least once per 3 months during the third year, and once per 6 months thereafter. Radiological examinations including CT and/or MRI of the head and neck were done at least twice within 6 months immediately after treatment, and at regular intervals of 6 to 12 months thereafter. Positron-emission tomography was not routinely done in this protocol. Time-to-event analyses from the start of RT were done using Kaplan–Meier estimates. Biopsy-proven recurrence of the primary tumor was considered as an event for calculating the local control rate, and patients who died without this event were censored at the time of last follow-up examinations. Death of any cause was defined as events in calculating overall survival. Also, recurrence at any site or death of any cause was used in estimating progression-free survival. Adverse events were estimated according to the National Cancer Institute Common Toxicity Criteria, version 2.0, and Radiotherapy Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring Scheme.

Although not required in the protocol, volumetry of the primary tumor was estimated from CT scans during RT planning in all patients retrospectively using RT planning software (Xio, version 4.4, Elekta CMS Software, St. Louis, MO) by the principal investigator (M.K.).

RESULTS

Patients. Between October 2002 and March 2008, 35 patients were enrolled. Patient characteristics are listed in Table 1. Thirteen of 15 patients with T3/4 disease had fixation of the vocal cord at presentation, and disease in 2 patients was defined as T3 because of estimated tumor diameter on CT/MRI scan that exceeded 4 cm. Among 20 patients with node-positive disease, 3 had lymph node metastasis at level IV, and the others were confined to level II and/or level III. Two patients had histories of esophagectomy due to esophageal cancer at 7 and 10 years before enrollment, and 2 other patients had simultaneous superficial esophageal cancers that were successfully treated with endoscopic mucosal resections thereafter. Three patients were classified as Zubrod PS 2, otherwise all patients were PS 1. At the time of this analysis, 1 patient was lost to follow-up at 24 months without evidence of disease recurrence. Otherwise, all patients were followed for more than 2 years or until death, and the median follow-up period for surviving patients was 59 months (24–90 months).

Table 1. Patient characteristics.

Characteristics	No. of patients	%
Sex		
Male	32	91
Female	3	9
Age		
Median (range), y	61 (46–73)	
Subsite		
Pyriform sinus	30	86
Post cricoid	4	11
Posterior wall	1	3
Differentiation		
Moderately	17	49
Poorly	6	17
Not specified	12	34
T/N classification		
T2	20	57
N0	7	20
N1	3	9
N2a	1	3
N2b	8	23
N3	1	3
T3	12	34
N0	6	17
N1	1	3
N2a	1	3
N2b	4	11
T4	3	9
N0	2	6
N1	1	3
Stage		
II	7	20
III	10	29
IV	18	51
Volume of the primary tumor (mL)		
Median (range)	15 (3–49)	
<10	5	14
≥10, <20	17	49
≥20, <30	9	26
≥30	4	11

Completeness of the Protocol. Eight patients received up-front nodal dissection at 8 to 25 days (median, 17 days) before start of RT without serious postoperative complications. All of the 35 patients

completed RT and chemotherapy as planned with a median overall treatment time of 44 days (range, 40–48 days). All prolongations of overall treatment time for more than 6 weeks were due to public holidays and/or maintenance of the RT machine. Adverse events that were observed within 90 days after start of the treatments are listed in Table 2. It should be noted that all of the grade 3 adverse events were observed after the end of the treatment and no patients required interruption of RT and/or chemotherapy. Five patients required transient parenteral hyperalimentation to supplement decreased oral intake. However, 24 (69%), 33 (94%), and 35 (100%) patients recovered their normalcy of diet within 2, 4, and 7 weeks, respectively, after completion of the treatments. Although 3 patients required tracheostomy before start of the treatments because of tumor-related airway stenoses, all of them were able to achieve complete resolution of the tumor and were decannulated within 2 months after completion of the treatments. One patient experienced transient grade 3 thrombocytopenia immediately after completion of RT but recovered spontaneously within a week without suffering a symptomatic hemorrhagic accident.

Patterns of Failure. Four patients experienced local persistence or recurrence with (n = 3) or without (n = 1) nodal metastases. Otherwise, 3 patients, all of whom had node-negative disease at presentation, experienced nodal recurrences as first sites of relapses within irradiated volume of the boost RT in 2 patients, and at the periphery in 1 patient. All but 1 patient with unresectable, isolated nodal failures underwent successful salvage without serious postoperative complications. However, 1 patient died of subsequent nodal failure. Two other patients experienced distant metastases in the lungs as first site of relapse without evidence of locoregional recurrence. Both of these 2 patients originally had node-negative disease (T2 in 1 patient and T4 in 1 patient). One patient died of ischemic heart disease without evidence of disease recurrence at 41 months. Overall survival rate at 3 years was 91% (95% confidence interval, 81% to 100%). All of the disease recurrences at the primary sites were observed within 2 years, and local control rate at 2 years was 88% (79% to 99%), as shown in Figure 1. Nodal and distant metastasis rates at 2 years were 14% (3% to 26%) and 6% (0% to 15%), respectively. Progression-free survival at 2 years was 77% (63% to 91%). All of the 20 patients who had T2 disease did not experience local recurrence. However, 1 patient died of nodal recurrence at 13 months. On the other hand, 4 of the 15 patients who had T3/4 diseases experienced local recurrences. Local control rate at 2 years for patients with T3/4 disease was 73% (51% to 96%).

Table 2. Acute events.

Grade	0	1	2	3	4	5
White blood cell	18	12	5	0	0	0
Anemia	25	6	4	0	0	0
Thrombocytopenia	33	0	1	1	0	0
Mucositis due to radiation	0	6	17	12	0	0
Dysphagia-pharyngeal due to radiation	1	8	18	8	0	0
Creatinine	24	10	1	0	0	0
Nausea/vomiting	31	2	2	0	0	0
Worst overall	0	4	18	13	0	0

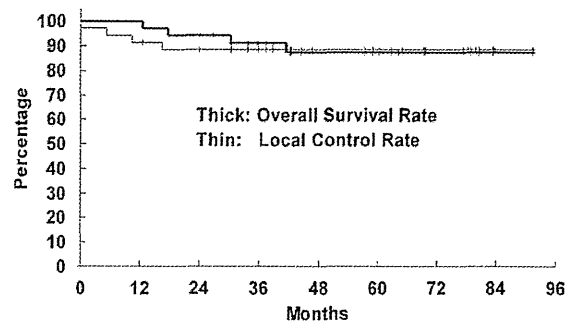

FIGURE 1. Kaplan–Meier estimates of overall survival and local control rates in patients with T2 to 4 primary tumor that was amenable to margin-free resection without bilateral or unresectable nodal metastasis who underwent chemotherapy-enhanced accelerated radiotherapy. Thick and thin lines represent overall survival and local control rates, respectively.

Primary tumors that showed superficial spread with an exophytic growth pattern had tumor volumes of less than 7 mL (n = 5), whereas patients that presented with endophytic tumors (n = 30) had tumor volumes of at least 10 mL on CT volumetry. Local control rate at 2 years for the former patients was 100%, contrasted to 87% (95% confidence interval, 74% to 99%) for the latter.

Late Adverse Events. One patient required 3 months of gastrostomy tube feeding and antibiotics for exposure of the thyroid cartilage to the pharyngeal cavity at 10 months, and another patient underwent repetitive balloon dilatation for pharyngeal stenosis without the need of taking a soft diet at 9 months. Both patients recovered their normalcy of diet thereafter and were alive and recurrence-free at 83 and 58 months, respectively. Otherwise, late radiation morbidities of grade 2 or greater were not observed. As a whole, all of the patients who were alive with their larynx retained their normal understandable speech without the need for a tracheostomy. Furthermore, all patients who were alive, including those who underwent salvage total laryngopharyngectomy, maintained their normal diets.

DISCUSSION

For laryngeal cancer, a clinical practice guideline for larynx-preserving approach was presented[17] based on

data accumulated from landmark studies.[25,26] The same principles are thought to be applicable to hypopharyngeal cancer. In this study, patients who had primary tumors that mostly localized within the hypopharynx and larynx without penetration of the thyroid cartilage and pharyngeal constrictor muscle were enrolled. These hypopharyngeal cancers had tumor volumes of approximately $\leq$30 mL, and better local control rate after RT than in patients with larger primary tumors as was suggested from retrospective studies.[19,27,28] Measurement of tumor volume is significantly influenced by interobserver variation and imaging modality used in volumetry.[29] However, the required precision for tumor volumetry to adequately predict radiocurability was considered as $\pm$50% in a review of the literature.[30] Therefore, it is conceivable that most patients enrolled in this study had "intermediate-volume" tumors requiring total laryngopharyngectomy as a curative surgical approach and amenable to margin-free resections, but which were not categorized as having "low-volume" tumors.

When this study was being developed, however, a high percentage of patients with intermediate-volume hypopharyngeal cancers without advanced nodal diseases did not receive definitive CRT in many academic centers in Japan.[1,31] This was because the safety and efficacy of possible salvage surgery after CRT was empirically expected to be poor.[32,33] In addition, a recent multiinstitutional larynx-preserving trial using intensive CRT showed that, at 1 year, 23% of the patients were able to swallow only soft foods or liquids, and 3% could not swallow at all.[26] Other detrimental effects of concomitant high-dose chemotherapy with altered fractionation RT on long-term swallowing functions were also documented.[34,35] For patients with hypopharyngeal cancer with intermediate-volume primary tumors, clinical clarification of the following points were sought in this study: (1) altered fractionation RT alone is insufficient to satisfy the result; (2) however, 2 or more courses of concomitant chemotherapy not only could result in deterioration of function, but is unnecessary to achieve the outcome comparable to altered fractionation RT alone for early-stage, low-volume tumors[10,11]; (3) efforts to minimize the irradiated volume receiving CRT may be needed to prevent excessive vascular and/or connective tissue damage at the expected anastomosis site in possible salvage surgery; (4) for this purpose, up-front nodal dissection should be positively considered in patients with nodal disease spreading outside of the target volume for boost RT encompassing only the primary tumor with margins. Concomitant chemotherapy during the former part of RT was not done to eliminate unexpected local and/or systemic toxicity of chemotherapy that possibly interrupt timely administration of accelerated RT.[21] As a result, all patients completed the protocol treatment without an unplanned break, and all of the 4 patients who experienced local recurrences safely underwent salvage total laryngopharyngectomy.

More than 5 years were required to accumulate the 35 patients as expected at the time of protocol development. The principal conclusion of this study was the feasibility of this protocol. However, it should be emphasized that none of the 20 patients with T2 disease experienced local recurrence. Although 73% of local control rate at 2 years for T3/4 disease was observed in only 15 patients, the lower limit of the 95% confidence interval was 51%, which exceeded the results of a previous randomized study for larynx-preserving treatment in patients with resectable hypopharyngeal cancer.[3] Overall survival rate at 3 years was 91% with acceptable distant failure rate. These results showed that this regimen can become an alternative to more intensive CRT in patients who were eligible for this study.

This regimen is in contrast to the widely accepted benefit of concomitant chemotherapy delivered throughout RT. However, for certain patients with stage III/IV disease, low-volume disease could achieve satisfactory results after treatment without using intensive chemotherapy.[14,36] Incidence of grade $\geq$3 mucositis was 34% (12 of 35), which was comparable to results in previous studies regarding CRT with higher dose of chemotherapy.[26] However, it should be noted that all of the grade 3 mucositis occurred after completion of the protocol and most of the patients recovered their normalcy of the diet within 4 weeks, probably because of no additional injury to the mucous membrane after occurrence of serious mucositis in this regimen. In addition, grade $\geq$3 hematologic toxicity was observed in only 1 patient (3%). Given that bacterial colonization in patients with compromised immune reaction aggravates and prolongs severe acute mucositis,[37] lower bone marrow toxicity of this regimen is preferable to ameliorate chronic dysphagia as a consequential late effect.[16] As a result, no surviving patient experienced feeding tube dependency at $\geq$2 years in this study. Upfront nodal dissection followed by definitive RT with or without substandard chemotherapy for appropriately selected patients with small pharyngolaryngeal cancer with bulky N2/3 disease could achieve locoregional control rates equal to those who had N0/1 disease without compromise of survival.[38–41] Six percent of distant failure rate (none in patients who underwent up-front nodal dissection) in this study was in good agreement with these previous reports.[38,40,41] The survival benefit of adding intensive chemotherapy for the purpose of preventing distant failure had never been observed in patients with resectable disease and, at present, the value of intensive chemotherapy for these patients is recognized as improvement of locoregional control.[3,12,26] In this context, because of 88% preservation rate of functioning larynx with a low distant failure rate, this study including 20 patients with node-positive disease who were amenable to margin-free resections (8 required up-front nodal dissection)

should not be criticized based solely on substandard use of chemotherapy. Involvement of nodal metastasis outside of the sentinel area (ie, ipsilateral levels II and III) was reported as a significant factor of developing distant failure.[42] Because only 3 of 35 patients had gross nodal disease at the level IV, the results of this study might be relevant to a subsection of hypopharyngeal cancer patients having T2 or small T3/4 primary tumor with N0 to resectable N2 disease localized to the sentinel area (incipient N2), which should be considered in subsequent studies. The necessity of upfront nodal dissection only for prevention of excessive tissue damage may be negated in the intensity-modulated radiotherapy era.

Whether the results of this study were merely due to our patient selection in a single institutional setting, must be elucidated in larger, multi-institutional trials. However, the survival benefit of altered fractionation RT was already demonstrated in a meta-analysis.[43] Patients with hypopharyngeal cancer have relatively poor health status and high propensity of developing acute and/or late toxicities such as pneumonia and dysphagia. In this context, the benefit of intensive chemotherapy added to RT may be diminished and negated by its toxic effect when patients with hypopharyngeal cancer having relatively small tumor burdens are included in larynx preserving trials.[30] Therefore, testing separate strategies for patients with intermediate-volume primary tumor with N0 to incipient N2 disease was considered justifiable. Appropriateness of chemotherapy-enhanced accelerated RT was thought to be applicable even when intermediate-volume tumors were categorized as T3/4 disease in the current staging system with sophisticated imaging modalities. However, dosing of chemotherapy, role of induction chemotherapy, and molecular targeted therapy should be studied further with careful patient selection in these patients. In patients who have larger tumor burdens, reduced dose chemotherapy no longer achieved satisfactory tumor cure.[44,45]

In conclusion, accelerated fractionation RT with delayed concomitant chemotherapy as a radiation sensitizer was feasible and showed encouraging oncological and functional outcomes in patients with intermediate volume hypopharyngeal cancer who would otherwise have required total laryngopharyngectomy. Further study is warranted to test the appropriateness of this regimen for patients with hypopharyngeal cancer who have intermediate-volume, especially T2, primary tumor with N0 to incipient N2 disease in multi-institutional collaborations.

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Concomitant Weekly Cisplatin and Radiotherapy for Head and Neck Cancer

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Objective: The most common chemoradiotherapy regimen is high-dose (100 mg/m^2) three-weekly cisplatin with concomitant radiotherapy; however, this protocol is associated with acute and late toxicities. Here, we reviewed the dose intensity and toxicity for concomitant weekly cisplatin and radiotherapy in patients with head and neck cancer.

Methods: Fifty-three patients with untreated head and neck cancer were enrolled and evaluated at our institution from April 2006 to April 2010. Weekly cisplatin (40 mg/m^2) was given on weeks 1, 2, 3, 5, 6 and 7 with radiotherapy, which comprised a standard dose of 70 Gy delivered in 35 daily fractions over 7 weeks.

Results: Fifty-one patients (96.2%) received the full dose of radiotherapy, while the course was disrupted by adverse events in two. Over the course of the chemotherapy, 31 patients (58.5%) received more than 200 mg/m^2 cisplatin. The toxicity was manageable in all except one patient, who died of sepsis after completing treatment. The 2-year overall survival rate and local progression-free rate for all patients were 93.7% and 88.0%, respectively. The primary site showed a complete response in 52 patients (98.1%) and a partial response in 1 patient (1.9%). The primary disease was well controlled by chemoradiotherapy in 47 patients (88.7%).

Conclusions: Weekly cisplatin could be easier to manage than three-weekly cisplatin, because patients can be monitored more regularly for toxicity allowing the schedule to be altered if required. This regimen appears to be a suitable alternative to three-weekly high-dose cisplatin with concomitant radiotherapy.

Key words: chemotherapy – cisplatin – radiotherapy – chemoradiotherapy

INTRODUCTION

Locoregionally advanced head and neck cancer (HNC) is generally treated with surgery followed by postoperative radiotherapy (RT). However, definitive concomitant chemoradiotherapy (CRT) is an alternative treatment option (1). Cisplatin is the most common agent used in combination with RT, and is one of the best studied. The standard regimen is three-weekly high-dose (100 mg/m^2) cisplatin (three cycles) concurrent with RT (2,3).

However, cisplatin at a dose of 100 mg/m^2 with concomitant RT is associated with significant acute and late toxicities (2,4,5). Furthermore, the completion rate for this regimen is relatively poor (2,3). The use of a lower cumulative cisplatin dose or a more fractionated cisplatin dose has therefore been suggested (6–8).

Renal function has been reported to decrease rapidly with aging in the Japanese population, although the underlying reason remains unclear (9). The recommended dose of cisplatin is 60–70 mg/m^2 for patients with HNC according to

the Japanese Ministry of Health, Labor and Welfare. A retrospective study of three Japanese patients with nasopharyngeal cancer receiving cisplatin and concurrent RT reported severe acute toxicities (10). By contrast, weekly cisplatin at a dose of 40 mg/m^2 was found to be well tolerated and to have acceptable toxicity, despite the large RT fields employed, for the treatment of nasopharyngeal carcinoma (11).

Weekly cisplatin at a dose of 40 mg/m^2 has been the standard schedule for HNC at our institution since 2006. In the present study, we calculated the dose intensity and evaluated the toxicity of this regimen in patients with HNC at our institution retrospectively.

PATIENTS AND METHODS

Patients

To be eligible for inclusion in this study, patients were required to have histologically proven Stage II–IV carcinoma of the oropharynx, hypopharynx or larynx. All patients were 75 years of age or younger, and had not received previous treatment for the tumor except neck dissection. Patients were required to be free of other active cancers, as well as distant metastases, and to meet the following criteria: a World Health Organization performance status of 0–2; a white-cell count of at least 4000/mm^3; a platelet count of at least 1 00 000/mm^3; a hemoglobin concentration of at least 9.5 g/dl; serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase levels of less than twice the upper limit of the normal range; a total bilirubin concentration of $<$2.0 mg/dl; a serum creatinine concentration of $<$1.5 g/dl; a blood urea nitrogen concentration of $<$25 mg/dl; and a creatinine clearance of more than 60 ml/min. The disease had to be measurable or amenable to evaluation, and had to be documented as precisely as possible before treatment by endoscopy, including computed tomography (CT) and/or magnetic resonance imaging (MRI). All patients were initially evaluated by a multidisciplinary team consisting of otolaryngologists and radiation oncologists, and the tumors were classified according to the 2002 Union Internationale Contre le Cancer (UICC) staging system. Written informed consent was obtained from all patients before entry into the study. Patients who were pregnant or breast-feeding were excluded from the study.

Chemotherapy

Weekly cisplatin was administered at a dose of 40 mg/m^2 on weeks 1, 2, 3, 5, 6 and 7 of the RT. Patients received prophylactic hydration (4 l) and $5HT_3$ antagonists plus dexamethasone for anti-emetic prophylaxis. The intended maximum total dose of cisplatin was 240 mg/m^2. The cisplatin dose was modified on a case-by-case basis according to the level of leucopenia and/or thrombocytopenia, the serum creatinine and/or creatinine clearance, the presence of liver dysfunction and/or infectious disease, and the patient's wishes. In addition, weekly cisplatin was altered to weekly carboplatin [area under the curve (AUC) = 1.5] in some cases based on the toxicity.

Preparation for percutaneous endoscopic gastrostomy feeding before treatment was recommended. The use of non-steroidal anti-inflammatory drugs was avoided, in order to prevent any synergistic toxic effects with cisplatin on renal function.

Radiotherapy

A standard dose of 70 Gy was delivered in 35 daily fractions over 7 weeks to all of the patients. All of the patients received external RT (40 Gy/20 fractions/4 weeks), in the form of 4 or 6 MV photons produced by a linear accelerator, to the primary sites and regional lymphatic area. The treatment was planned using a CT simulator and a three-dimensional dose-calculation computer. For patients who were suspected of having lymph-node metastases, the lower-neck region and supraclavicular fossa were prophylactically irradiated with a total of 40 Gy using an anterior single port. Electron beams were used to boost the dose delivered to the posterior cervical lymph nodes. The dose delivered to the spinal cord was kept below 40 Gy in all instances. After the initial dose of 40 Gy had been administered, an additional dose of 30 Gy was given with a shrunken field in 15 fractions over 3 weeks.

Evaluation of Toxicity and Response

Toxicities were graded using the Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 3.0. For measurable lesions, responses were evaluated by clinical examination and/or CT or MRI studies 6–8 weeks after the completion of therapy using the Response Evaluation Criteria in Solid Tumors (RECIST). CT and MRI were performed 6–10 weeks after the end of RT as a convenient means of determining target-lesion progress and identifying emerging new lesions.

Positron-emission tomography (PET) and PET-CT were used to support the diagnosis. Based on the radiographic changes related to treatment, it can be difficult to distinguish between the scar tissue and residual tumor tissue. Over time, however, the scar tissue will remain stable, whereas the remaining tumor tissue can progress. We designed the patient outcomes to reflect this uncertainty: a patient with radiological changes that remained stable over time, and no signs or symptoms of disease, was considered to be 'progression free'. Biopsy was performed only to document recurrence when indicated.

Statistical Considerations

Data on the disease site, Tumor-Node-Metastasis (TNM) stage, RT dose/fractionation and chemotherapy regimen were

collected. Incidences of delays to therapy, acute toxicity, dose reduction and missed treatments for both chemotherapy and RT were also recorded.

The primary endpoint was treatment compliance. Complete treatment delivery was defined as the administration of the 70 Gy RT dose within 63 days, and the completion of five or six courses of cisplatin. Treatment compliance was evaluated based on the rate of complete treatment delivery.

Cases of persistent or recurrent primary disease after the completion of CRT were considered to be local failures unless salvage was successful. The probabilities of overall survival, which included death from any cause, and the local control rates (the local progression-free rates computed from the beginning of treatment until the time of local relapse) were calculated by the Kaplan–Meier method.

RESULTS

Patient Characteristics

Fifty-three patients (49 males and 4 females) were enrolled in the study and were evaluated from April 2006 to April 2010 (Table 1). The patients ranged in age from 40 to 75 years (median = 62 years). The most common site of the primary disease was the hypopharynx (22 patients), followed by the oropharynx (18 patients), larynx (12 patients) and oral cavity (1 patient). Two patients underwent bilateral neck dissection prior to CRT. One patient with T2N2b laryngeal cancer and synchronous esophageal cancer underwent esophagectomy and bilateral neck dissection prior to CRT in order to preserve the larynx. One patient with unknown primary bilateral neck cancer underwent bilateral neck dissection and panendoscopy with biopsies of the pharynx. A pathological examination revealed the base of the tongue as the primary site in this case, and the patient subsequently underwent CRT.

The clinical stages are listed in Table 2. In total, 30 patients had Stage IV disease, 6 had Stage III disease and the remaining 17 had Stage II disease.

All of the patients were closely observed during follow-up. The follow-up period of survivors ranged from 7 to 57 months (median = 29 months; mean = 29 months).

Table 1. Clinical characteristics ($n = 53$)

Age (years)	
Range	40–75
Median	62
Mean	61.1
Sex	
Male	49 (92.5%)
Female	4 (7.5%)
Performance status	
0	39 (73.6%)
1	12 (22.6%)
2	2 (3.8%)
Primary tumor site	
Oral cavity	1 (1.9%)
Oropharynx	18 (34.0%)
Hypopharynx	22 (41.5%)
Larynx	12 (22.6%)
Histology	
Squamous cell	51 (96.2%)
Adeno	1 (1.9%)
Lymphoepithelial	1 (1.9%)

Table 2. T and N stage ($n = 53$)

T stage	N stage						
	0	1	2a	2b	2c	3	Total
1		1		1	2		4
2	17	1		10	2	1	31
3	2	2	1	9		1	15
4a	1			1			2
4b				1			1
Total	20	4	1	22	4	2	53

Adverse Events

The acute adverse events observed, including hematological and non-hematological toxicities, are summarized in Table 3. One patient died of sepsis after completing the treatment; this patient exhibited Grade 3 leucopenia, anemia, fever and renal dysfunction, and Grade 4 thrombocytopenia, liver dysfunction and hypernatremia. Grade 4 hematological toxicities were not observed among the other patients. Grade 3–4 mucositis was observed in 21 patients (39.6%). Mild-to-intermediate renal dysfunction was observed in 15 cases: Grade 1 creatinine was present in 13 patients (24%), Grade 2 in 1 (2%) and Grade 3 in 1 (2%). The other Grade 3–4 non-hematological side effects observed included nausea/vomiting ($n = 3$), liver dysfunction ($n = 3$), dermatitis ($n = 18$), fever ($n = 4$), hyponatremia ($n = 1$), hypernatremia ($n = 1$), appetite ($n = 8$) and hyperglycemia ($n = 1$). None of the surviving patients showed evidence of disease, and all except one were able to achieve oral intake without feeding-tube support. Pharyngeal stenosis occurred in one patient with T3N1 hypopharyngeal cancer, who suffered from repeated pneumonia and underwent a total laryngopharyngectomy and free-jejunum transfer. One patient experienced osteonecrosis of the mandible, but did not require surgical treatment.

Total Treatment Compliance

In total, 51 of the patients (96.2%) received the full dose of RT (70 Gy) over a median period of 50 days (range = 46–62 days). The radiation course was disrupted in two of the patients by adverse events. The reasons for extension of the RT course beyond 50 days were holidays and machine maintenance, except in two patients. A total of 34 patients (64.2%) completed five (15 patients) or six (19 patients) courses of the chemotherapy; 11/17 (64.7%) with Stage II and 23/36 (63.9%) with Stage III/IV. However, in three of these patients, the dose of cisplatin was modified due to adverse effects. As a result, 31 patients (58.5%) received more than 200 mg/m^2 of cisplatin. The cisplatin treatment was stopped in 2 patients (3.8%) after one course, in 3 patients (5.7%) after two courses, in 4 patients (7.5%) after three courses and in 10 patients (18.9%) after four courses. Four of the five patients who received only one or two courses of cisplatin were switched to weekly carboplatin (AUC = 1.5). Finally, the average total amount of cisplatin administered was 185 mg/m^2 (median = 190 mg/m^2) when data from all patients were included in the analysis, and the average dose intensity of cisplatin was 26.5 mg/m^2/week.

Table 3. Toxicity ($n = 53$)

Toxicity	Grade				
	1	2	3	4	5
Leucopenia	11	23	14		
Neutropenia	10	17	10		
Anemia	22	17	9		
Thrombocytopenia	12	5	1	1	
Nausea/vomiting	14	4	3		
Mucositis	4	21	17	4	
Febrile neutropenia			2		1
Renal dysfunction	13	1	1		
Liver dysfunction	7	4	2	1	
Dermatitis	10	19	18		
Fever	16	2	4		
Appetite	22	3	8		
Hyponatremia	1		1		
Hypernatremia				1	
Hyperkalemia	2				
Hyperglycemia				1	
Hypercalcemia	1				

Overall Survival and Local Control

The 2-year overall survival and local progression-free rates for all patients were 93.7% and 88.0%, respectively (Fig. 1).

Response of the Primary Disease

Of the 53 patients who entered into the treatment program, complete responses at the primary site were observed in 52 (98.1%) and partial responses in 1 (1.9%). The primary disease was well controlled by CRT in 47 patients (88.7%). The remaining six patients (11.3%) had persistent or recurrent primary disease after completing CRT. All six of these patients underwent salvage surgery, and four subsequently survived and remained disease-free.

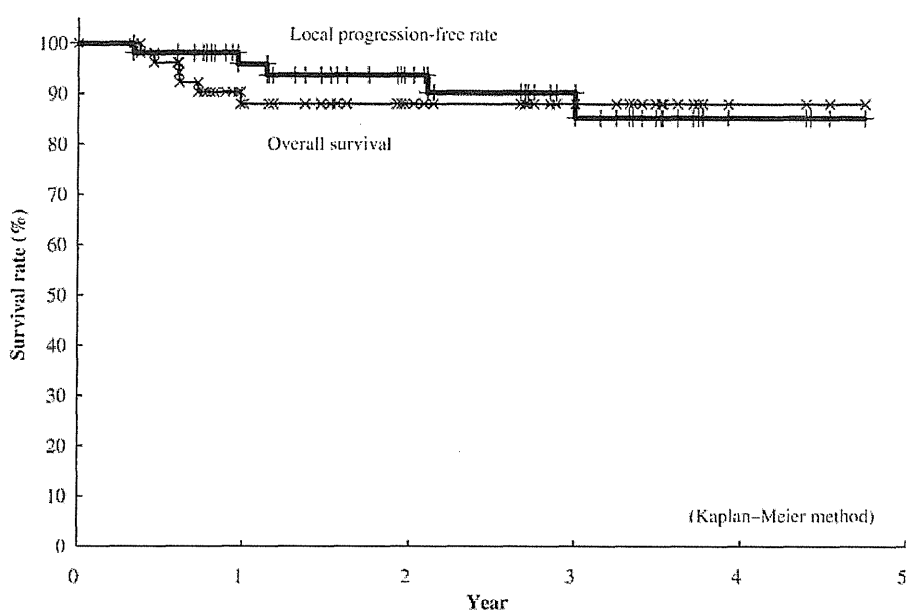

Figure 1. Overall survival and local progression-free rates.

Response of Neck Disease

Among the 33 patients with positive neck disease, two underwent neck dissection prior to CRT. Among the remaining 31 patients, the disease was well controlled by CRT without surgery in 20 patients (64.5%). Eight patients with obvious or suspected persistent neck disease after CRT were treated successfully by salvage neck dissection. In four of these patients, no viable cancer cells were observed in the surgical specimens. One patient with persistent neck disease after CRT received chemotherapy, which successfully treated the disease. Two patients underwent neck dissection when they received salvage surgery for recurrent primary disease. Both patients had no viable cancer cells in the surgical specimens, but one had recurrence in the primary and neck lesions. Thus, in 25 of the 31 patients (80.6%), the positive neck disease was well controlled by CRT. At the time of writing, 32 of the 33 patients had successfully controlled disease.

Sites of Uncontrolled Recurrence

The site of uncontrolled recurrence was identified whenever possible. Uncontrolled recurrence initially occurred at distant metastases in four patients, at the primary site in one patient and at the primary site and regional lymph nodes in one patient. One patient died of leukemia without recurrence in the head and neck region.

DISCUSSION

Three-weekly cisplatin at a dose of 100 mg/m^2 concurrent with RT is considered to be the standard of care for the non-surgical treatment of advanced HNC, based on several Phase III trials (2,3). However, this protocol has been associated with significant acute and late toxicities (2,4,5). Furthermore, the completion rate of this regimen has been reported to be relatively low, with 63–85% of patients in the CRT arm completing all three of the planned cycles of concurrent chemotherapy in several clinical trials (2,3,5). Poor compliance over three cycles of high-dose cisplatin was also reported in a series of patients at the Princess Margaret Hospital in Toronto. In this retrospective study of 75 patients, 42.7% underwent all three planned cycles of chemotherapy, and only 33.3% received the intended dose without a cumulative delay of at least 7 days throughout the three cycles (12). The death rate for patients undergoing this protocol was reported to be 4–5% in Phase III trial (2,3,13), and 10% in the community setting (13).

Ho et al. (14) retrospectively compared the differences in dose intensity, delays and toxicity between weekly and three-weekly cisplatin administered concurrently with RT to patients with locally advanced HNC. The authors concluded that three-weekly cisplatin at a dose of 100 mg/m^2 concurrent with RT was less well tolerated than weekly cisplatin at a dose of 40 mg/m^2, and resulted in less patients achieving a cumulative dose of more than 200 mg/m^2, thereby potentially lowering the chemotherapy dose intensity. Based on these results, high-dose cisplatin might not be suitable for routine use.

The Head and Neck Intergroup conducted a Phase III randomized trial comparing radiation therapy alone with radiation and concurrent weekly cisplatin at a dose of 20 mg/m^2 between 1982 and 1987 (15). Although the response rate was greater in patients treated with the concurrent regimen, the median survival was only 13 months and did not differ between the two treatment arms. Although the addition of concurrent weekly cisplatin at 20 mg/m^2 to daily radiation did not significantly improve survival, there was some evidence of an effect. Similarly, concomitant CRT using daily low-dose (4 mg/m^2) cisplatin showed disappointing results (16). A high dose of cisplatin was therefore considered necessary to achieve a good outcome (17,18).

CRT using weekly cisplatin at a dose of 40 mg/m^2 was found to be well tolerated in patients with advanced nasopharyngeal carcinoma in Hong Kong (11). The relatively low dose used in the investigation arm of the study resulted in no treatment-related mortalities, although this strategy could have led to suboptimal benefits. The progression-free survival rate significantly differed between the concurrent CRT arm and the RT-alone arm for patients with advanced T and N stages. Hence, after some consideration, we introduced this schedule at our institution.

The regimen appeared to be well tolerated, with low rates of severe toxicities: 62.3% of the patients completed at least five of the six planned chemotherapy cycles. A total cisplatin dose of 200 mg/m^2 or more was delivered to 58.5% of the patients in this study. The average dose intensity of cisplatin (26.5 mg/m^2/week) was equivalent to that of three-weekly regimen (28.9 mg/m^2/week) (19). With regard to toxicity, the rate of Grade 3 or greater leukopenia and mucositis in the three-weekly cisplatin regimen in patients with unresectable disease was reported to be 42.1% and 45.2%, respectively. Also in the same regimen for laryngeal preservation, the rate of Grade 3 or greater hematologic toxicity and mucositis was 47% and 43%, respectively. In the present study, the rate of Grade 3 or greater leukopenia and mucositis was 26.4% and 39.6%, respectively. Toxicity in the present study was similar or less than those in Phase III trial of three-weekly cisplatin regimen.

Weekly cisplatin could be easier to manage than three-weekly cisplatin because patients can be more regularly monitored for toxicity, and the schedule can be changed before the effects become severe, based on the patient's condition. Because the dose delivered in each cycle is smaller, the toxicity is reduced. In the current study, five of the patients stopped receiving cisplatin after one or two courses due to the toxicity. Four of these patients subsequently received weekly carboplatin (AUC = 1.5) instead of cisplatin: creatinine clearance measured by the Cockcroft–Gault formula dropped to $<$50 ml/min in three patients, Grade 3 liver dysfunction was present in the fourth patient. If these patients, who were considered unsuitable for cisplatin administration, had initially

received a dose of 100 mg/m^2, the toxicity would have been more serious and they might have not undergone further chemotherapy or RT. We therefore consider this regimen to be a reasonable alternative to three-weekly high-dose (100 mg/m^2) cisplatin concurrent with RT.

Molecular growth inhibitors such as cetuximab have recently been investigated in conjunction with radiation therapy for advanced HNC patients, and have shown promising results (20–22). The Memorial Sloan-Kettering Cancer Center reported a Phase II trial of concomitant boost RT, cisplatin (100 mg/m^2 in weeks 1 and 4) and cetuximab (400 mg/m^2 intravenously in week 1, followed by 250 mg/m^2 in weeks 2–10). The study was halted owing to significant adverse events, including two deaths (one from pneumonia and one from unknown causes), one case of myocardial infarction, one case of bacteremia and one case of arterial fibrillation (21). Cisplatin at a dose of 100 mg/m^2 concurrent with radiation therapy is an intensive regimen, and adding a molecular-targeted agent might have resulted in the unacceptable toxicity. The results of the French TREMPLIN trial indicated that only 43% of all patients receiving induction docetaxel, cisplatin, and 5-fluorouracil chemotherapy (TPF) followed by cisplatin (100 mg/m^2) CRT (Arm A) were compliant with the full course of treatment, in contrast to 74% of the patients receiving induction TPF and subsequent cetuximab-containing bioradiation (Arm B) (23). Three months after treatment, there was no significant difference in laryngeal preservation between Arm A (93%) and Arm B (96%). Further clinical trials of concomitant CRT using cisplatin with a molecular-targeted agent, with or without induction chemotherapy, are required.

In conclusion, it is unlikely that cisplatin at a dose of 100 mg/m^2 will be an acceptable standard CRT regimen because of the severe toxicity. However, radiation therapy concomitant with cisplatin is likely to remain a key regimen. Weekly cisplatin could be easier to manage than three-weekly cisplatin, because patients can be monitored more regularly for toxicity allowing the schedule to be altered if required. In addition, the average dose intensity of cisplatin of weekly regimen was equivalent to that of three-weekly regimen. Therefore, weekly cisplatin is predicted to play an important role in the future. We thus believe that there is a need for a randomized trial comparing high-dose (100 mg/m^2) three-weekly cisplatin and weekly cisplatin as a basic CRT regimen in the near future.

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Conflict of interest statement

None declared.

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