Title: Feasibility and efficacy of induction docetaxel, cisplatin, and 5-fluorouracil chemotherapy combined with concurrent weekly cisplatin chemoradiotherapy for locally advanced head and neck squamous cell carcinoma

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Abstract

Background: To evaluate the feasibility of induction docetaxel, cisplatin, and 5-fluorouracil chemotherapy followed by concurrent weekly cisplatin chemoradiotherapy for patients with locally advanced head and neck squamous cell carcinoma (HNSCC).

Methods: Between **2010** and 2013, 30 patients with Stage IV HNSCC were treated in Hokkaido University Hospital with three cycles of induction chemotherapy (docetaxel 75mg/m^2 and cisplatin 75mg/m^2, day 1; and 5-fluorouracil 750mg/m^2/day 120h continuous infusion, every 3 weeks) followed by concurrent weekly cisplatin (40mg/m^2, on weeks 1, 2, 3, 5, 6 and 7) chemoradiotherapy.

Results: Three courses of induction chemotherapy were performed in 25 patients (83%), with grade 3-4 toxicities during induction chemotherapy observed in 22 patients (73%). The major toxicities were hematologic, with 22 cases (73%) showing grade 3-4 neutropenia. Radiotherapy was completed (70Gy) in 29 patients (97%), while a total of 19 patients (63%) completed five (13 patients) or six (6 patients) courses of the chemotherapy. During concurrent chemoradiotherapy, no grade 4 hematological toxicities were observed. Grade 4 dermatitis was observed in one patient, and grade 3 mucositis was observed in 12 patients. There were no treatment-related deaths during

the induction chemotherapy or concurrent chemoradiotherapy. The 1- and 2-year progression-free survival and 1- and 2-year overall survival rates were 86%, 72%, and 89%, 81%, respectively.

Conclusion: Sequential therapy composed of induction chemotherapy followed by concurrent weekly cisplatin chemoradiotherapy is feasible, showing encouraging results in patients with locally advanced HNSCC. Concurrent weekly cisplatin chemoradiotherapy following induction chemotherapy appears to be a suitable alternative to three-weekly high-dose cisplatin therapy.

Mini Abstract

Sequential therapy composed of induction chemotherapy followed by concurrent weekly cisplatin chemoradiotherapy is feasible for and shows encouraging results in patients with locally advanced HNSCC.

Key Words: head and neck cancer, induction chemotherapy, chemoradiotherapy

Introduction

For the treatment of patients with locally advanced head and neck squamous cell carcinoma (HNSCC), concurrent chemoradiotherapy has been demonstrated to benefit survival in many clinical trials and the meta-analysis of chemotherapy in head and neck cancer (MAHC-NC) [1]. Concurrent chemoradiotherapy is applied to both patients with unresectable disease and patients with resectable disease who refuse radical surgery. Three-weekly cisplatin at a dose of 100 mg/m^2 is considered to be the standard treatment for patients with advanced HNSCC [2, 3]. However, this protocol has been reported to be associated with severe acute and late toxicities. Alternative cisplatin dosing schedules are sometimes used due to improved patient tolerance [4-6]. We previously reported that weekly cisplatin at a dose of 40 mg/m^2 was easier to manage than three-weekly cisplatin [7]. Although concurrent chemoradiotherapy reduces the rates of locoregional failure, distant metastases represent a major cause of treatment failure in the patients treated by concurrent chemoradiotherapy [8].

Induction chemotherapy has been added to chemoradiotherapy in an attempt to decrease the likelihood of distant metastasis, improve local regional control, and aid organ preservation [9]. Two Phase III trials that focused on the efficacy of induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (5-FU) (DCF) have shown

promising results [10, 11]. Cisplatin, carboplatin, docetaxel, cisplatin plus 5-FU, and cetuximab regimens have been reportedly used in concurrent chemoradiotherapy following induction chemotherapy [9, 10, 12, 13]. In our study, sequential therapy, consisting of induction chemotherapy involving three cycles of docetaxel and cisplatin plus 5-FU, followed by concurrent chemoradiotherapy with six cycles of weekly cisplatin and radiotherapy was administrated.

The objectives of this study were to evaluate the compliance, response rate and toxicities of the sequential therapy for patients with locally advanced HNSCC.

PATIENTS AND METHODS

Patients

We retrospectively identified 30 consecutive patients with previously untreated stage IV, M0 unresectable HNSCC of the oropharynx, hypopharynx, or larynx treated with curative intent at Hokkaido University by a regimen of induction chemotherapy followed by concurrent chemoradiotherapy between 2010 and 2012. The criteria for inoperability were technical unresectability, low surgical curability, and organ preservation. All patients were 70 years old or younger and had not received any previous treatment for the tumor. Patients were required to be free of other active

cancers as well as distant metastases. An Eastern Cooperable Oncology Group performance status of 0-1 was required in addition to the following criteria: a white cell count of at least 4,000/mm^3, a platelet count of at least 100,000/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 less than 2.0 mg/dL, a serum creatinine concentration of less than 1.5 g/dL, a blood urea nitrogen concentration of less than 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 head and neck surgeons, radiation oncologists, and medical oncologists. The tumors were classified according to the 2002 Union Internationale Contre le Cancer (UICC) staging system.

HPV typing by multiplex PCR

The HPV infection status for patients with oropharyngeal squamous cell carcinoma (OPSCC) was analyzed using multiplex PCR, which can detect 16 HPV

genotypes (types 6, 11, 16, 18, 30, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66), as described previously [14].

Induction Chemotherapy

Induction chemotherapy consisted of docetaxel at 75 mg/m^2 on day 1, cisplatin at 75 mg/m^2 on day 1, and 5-fluorouracil at a dose of 750 mg/m^2 by 24-hour continuous infusion for 5 days; three cycles at 21-day intervals were planned. All patients were given adequate hydration and anti-emetics (5-HT3 antagonists and dexamethasone and/or neurokinin-1 receptor antagonist).

Concurrent chemotherapy

After induction chemotherapy, concurrent chemoradiotherapy was initiated between 3-4 weeks after the last chemotherapy cycle. Weekly cisplatin was administered at a dose of 40 mg/m^2 on weeks 1, 2, 3, 5, 6 and 7 of the radiotherapy. Patients received prophylactic hydration and 5-HT3 antagonists plus dexamethasone and/or neurokinin-1 receptor antagonist for anti-emetic prophylaxis. The intended maximum total dose of cisplatin was 240 mg/m^2. Preparation for percutaneous endoscopic gastrostomy feeding prior to 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 radiotherapy (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 from CT scans of the neck and chest two weeks after the last course of induction chemotherapy and 6-8 weeks after radiotherapy using the Response Evaluation Criteria in Solid Tumors (RECIST).

Statistical Considerations

Data on 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, even if 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

Of the 61 HNSCC patients who fulfilled the eligibility criteria described in the PATIENTS AND METHODS section, 30 patients (27 males and 3 females) were enrolled in the study. Table 1 shows the patient and tumor characteristics. The patients ranged in age from 40 to 69 years (median=57 years). The most common site of the primary disease was the oropharynx (15 patients), followed by the hypopharynx (13 patients) and larynx (2 patients). The clinical stages are listed in Table 2. The number of the patients with Stage IVA and IVB disease was 24 and 6, respectively. The median follow-up period was 18 months (range, 5-38 months).

Of the 15 patients with OPSCC, HPV infection status was analyzed in 11. Six patients were found to be HPV-positive, with five positive for HPV16, and one positive for HPV18 (Table 3).

Induction chemotherapy

Of the 30 patients, 25 (83%) underwent three cycles of treatment at the planned doses. Three patients (10%) received two cycles, and 2 patients (7%) received only one cycle due to toxicity **(Table 3 and 4)**. **The median day of the administration of the second cycle of induction chemotherapy was Day 23 (range 21-30), and the median day of the administration of the third cycle of induction chemotherapy was Day 44 (range 42-58). No dose modifications were made in any patient.**

The toxicity of the induction chemotherapy is summarized in Table **5**. Grade 3-4 toxicities during induction chemotherapy were recorded in 22 patients (73%). The major toxicities were hematologic, with 22 cases (73%) of grade 3-4 neutropenia. Grade 3 diarrhea was observed in 3 patients (10%).

The overall response rate after induction chemotherapy was 83% (25/30) **(Table 3 and 4)**. Only one patient experienced tumor progression, due to the appearance of contralateral neck node metastasis, and bilateral neck dissection was required before concurrent chemoradiotherapy **(Case #16, Table 4)**. **Another patient with stable disease with regard to lymph nodes after induction chemotherapy underwent neck dissection followed by chemoradiation as the neck disease was considered to be incurable by chemoradiation (Case #7, Table 3).**

Concurrent chemoradiotherapy

Of the 30 patients, 29 patients received a full dose (70 Gy) of radiotherapy, with one patient receiving only 50Gy of radiotherapy after refusing to undergo further radiotherapy **(Case #6, Table 3)**. A total of 19 patients (63%) completed five (13 patients) or six (6 patients) courses of the chemotherapy, with 6 patients receiving four courses, 4 patients receiving three courses, and one patient receiving just two courses of the chemotherapy. **The average total dosage of cisplatin during radiotherapy was 185 mg/m^2 (median = 200 mg/m^2) (Table 3 and 4).**

Acute toxicities during the concurrent chemoradiation are summarized in Table **6**. No grade 4 hematological toxicities were observed. Grade 4 dermatitis was observed in one patient, and grade 3 mucositis was observed in 12 patients. There were no treatment-related deaths during the induction chemotherapy or concurrent chemoradiotherapy.

Response after completion of concurrent chemoradiotherapy (Table 3 and 4)

After completion of concurrent chemoradiotherapy, 26 patients (87%) achieved a complete response, and only 1 (3%) experienced disease progression **due to lung**

metastasis (Case #16, Table 4). Two patients who achieved PR or SD for the neck site with CR for the primary site later underwent salvage neck dissection for residual disease after chemoradiation (Case #5, Table 3 and Case #26, Table 4).

Outcomes

Progression-free survival and overall survival are shown in Figure 1. The 1- and 2-year progression-free survival and 1- and 2-year overall survival rates were 86%, 72%, and 89%, 81%, respectively. The 1- and 2-year progression-free survival as well as the 1- and 2- year overall survival rates were all 83.3%.

Of the patients with HPV-positive OPSCC, the 1- and 2-year progression-free survival and overall survival rates were both 83.3%. Of the patients with HPV-negative OPSCC, the 1- and 2-year progression-free survival and 1- and 2-year **overall survival rates were 100%, 60%, and 100%, 80%, respectively. There were no statistically differences in survival rates between the HPV-positive and HPV-negative patients.**

Discussion

This study shows that induction DCF chemotherapy followed by concurrent

weekly cisplatin chemoradiotherapy was feasible for the treatment of and well-tolerated by patients with locally advanced HNSCC.

Eighty percent of the patients in this study completed three courses of induction DCF chemotherapy with acceptable toxicity. The most common grade 3-4 toxicity was neutropenia (73%), with 27% experiencing febrile neutropenia during induction chemotherapy. In other studies on the use of DCF induction chemotherapy, the rate of grade 3-4 neutropenia was reported variously to be 31.5-83 % [10, 11, 15-17], and the rate of febrile neutropenia was reported to be 5.2-18% [10, 11, 15-17]. Even though our results are at the higher end of the previously reported rates, there were no treatment-related deaths during the DCF induction chemotherapy. The overall response rate of the induction chemotherapy was 83%. This response rate was similar to those of other studies on DCF induction chemotherapy.

In our study, weekly cisplatin concurrent chemoradiotherapy was administrated after induction chemotherapy. Sixty-three percent of patients received more than 200mg/m^2 of cisplatin after induction chemotherapy. We previously reported that 59% of patients received more than 200mg/m^2 of cisplatin when undergoing concurrent weekly cisplatin chemoradiotherapy [18]. These results suggest that the use of DCF induction chemotherapy does not prevent the use of concurrent weekly cisplatin

chemotherapy.

The treatment of several series of patients with a combination of DCF induction chemotherapy and cisplatin-based concurrent chemoradiotherapy has been reported. In the TREMPLIN study [13], concurrent cisplatin 100mg/m^2/3week was administrated. Forty-two percent of the patients received three courses of cisplatin, 42% received two cycles, and 13% received one cycle. Prestwich *et al*. [19] reported that concurrent cisplatin 100mg/m^2/3week was administrated after DCF induction chemotherapy. Five percent of the patients received three courses of cisplatin, 61% received two cycles, and 29% received one cycle. They concluded that compliance over the three courses of concurrent chemotherapy was poor. Weekly cisplatin might be more easily managed than three-weekly cisplatin as patients can be monitored for toxicity more regularly, and the schedule can be changed, based on the patient's condition, before the effects become severe.

There were no treatment-related deaths during the concurrent weekly cisplatin chemoradiotherapy, and the toxicities of the concurrent weekly cisplatin chemoradiotherapy were considered acceptable. No patients were observed with grade 3 or greater renal dysfunction. Pain control was achieved by using opioids in place of NSAIDs to avoid renal dysfunction and this may have attenuated the potential for

severe renal dysfunction. **Based on a multicenter phase II study, Zenda *et al*. reported that an opioid-based systemic control program during chemoradiation may be helpful in improving compliance with chemoradiation [20].** Grade 3 mucositis was observed in 40% of patients during the concurrent weekly cisplatin chemoradiotherapy. Many of the patients were provided with gastrostomies before radiation, and several reports have shown that gastrostomies also improved compliance of chemoradiotherapy [**20**-22]. These supportive procedures are necessary for successful concurrent cisplatin-based chemoradiotherapy.

The complete response rate after treatment was 86% in this study. In other studies using sequential therapy; i.e., DCF induction chemotherapy followed by concurrent chemoradiotherapy, the complete response rate was reported to be 50% by Paccagnella *et al*. [12] and 86% by Prestwich *et al*. [19]. Sequential therapy, therefore, appears to result in high response rates in locally advanced HNSCC.

In this study, 50% of the patients had oropharyngeal cancer, which is similar to the rates of oropharyngeal cancer patients in other studies. HPV-positive oropharyngeal cancer has been shown to respond better to chemotherapy and radiotherapy in comparison with HPV-negative oropharyngeal cancer. **We have previously reported that Japanese patients with HPV-positive OPSSC have markedly superior survival**

rates compared to those with HPV-negative OPSCC [14]. However, there were no differences in survival rates between the HPV-positive and HPV-negative patients in this study. We speculate that this was due to the small patient population and short follow-up period. RTOG 1016 is now underway to determine whether treatment can be de-intensified for HPV-positive OPSCC. However, several patients with HPV-positive OPSCC are known to develop distant metastasis. Spector *et al*. [23] reported that the OPSCC patients with matted nodes have a risk of distant metastasis. Although the value of induction chemotherapy prior to definitive concurrent chemoradiotherapy has not been firmly established, this sequential therapy should be considered for selected patients with locally advanced disease, including those with HPV-positive OPSCC.

In conclusion, induction docetaxel, cisplatin, and 5-fluorouracil chemotherapy combined with weekly cisplatin concurrent chemoradiotherapy is a feasible treatment for and has high rates of complete response in locally advanced HNSCC patients. While the role of sequential therapy remains inconclusive, this sequential therapy should be considered for patients with locally advanced HNSCC.

Conflict of Interest Statement

No author has any conflict of interest.

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Figure Legend

Figure 1: Overall survival (OS) and progression-free survival (PFS) rates.

Table 1 Patient Characteristics (n=30)

Age-yr		
	Median	57
	Range	40-69
Gender		Male 27 / Female 3
ECOG performance status, n (%)		
	0	2 (6.7)
	1	28 (93.3)
Site of primary tumor, n (%)		
	Oropharynx	15 (50)
	Hypopharynx	13 (43.3)
	Larynx	2 (6.7)
Overall stage of disease, n (%)		
	IVA	24 (80)
	IVB	6 (20)

Table 2 T and N classification

T	N classification						
classification	0	1	2a	2b	2c	3	Total
1				3			3
2				8	2	1	11
3				1	3	1	5
4a				3	4	1	8
4b				1	1	1	3
Total				16	10	4	30

Table 3 Summary of the induction chemotherapy and concurrent chemoradiotherapy in the patients with oropharyngeal squamous cell carcinoma

Case#	Age	Gender	Tumor subsite	HPV	T	N	Stage	No. of DCF cycles administered	Response after ICT		Total dosage of cisplatin during CRT (mg/m^2)	Response after CRT	
									primary	neck		primary	neck
1	61	M	Anterior wall	HPV16	1	2b	IVA	2	CR	PR	200	CR	CR
2	56	M	Lateral wall	HPV16	2	2b	IVA	3	PR	PR	160	CR	CR
3	40	M	Lateral wall	HPV16	2	2b	IVA	1	PR	PR	200	CR	CR
4	46	M	Lateral wall	HPV16	3	3	IVB	3	PR	PR	200	CR	CR
5	44	M	Lateral wall	HPV18	4b	2b	IVB	3	PR	PR	200	CR	PR
6	48	M	Lateral wall	HPV16	4b	2c	IVB	3	PR	PR	160	CR	CR
7	69	M	Anterior wall	negative	1	2b	IVA	3	PR	SD	120	CR	CR
8	68	M	Posterior wall	negative	3	2c	IVA	2	CR	PR	240	CR	CR
9	61	M	Posterior wall	negative	3	2c	IVA	3	CR	PR	200	CR	CR
10	57	F	Lateral wall	negative	4a	2b	IVA	3	PR	PR	120	CR	CR
11	64	M	Anterior wall	negative	4a	2c	IVA	3	PR	PR	200	CR	CR
12	64	F	Lateral wall	N/A	1	2b	IVA	3	CR	CR	120	CR	CR
13	57	M	Lateral wall	N/A	2	2b	IVA	3	CR	PR	120	CR	CR
14	48	M	Lateral wall	N/A	3	2c	IVA	3	CR	CR	200	CR	CR
15	46	M	Lateral wall	N/A	4a	2c	IVA	3	PR	PR	160	CR	CR

DCF docetaxel, cisplatin, and 5-fluorouracil, *ICT* induction chemotherapy, *CRT* chemoradiation, *N/A* not available

Table 4 Summary of the induction chemotherapy and concurrent chemoradiotherapy in the patients with hypopharyngeal and laryngeal carcinoma

Case#	Age	Gender	Tumor site	T	N	Stage	No. of DCF cycles administered	Response after ICT		Total dosage of cisplatin during CRT (mg/m^2)	Response after CRT	
								primary	neck		primary	neck
16	52	M	Hypopharynx	2	2b	IVA	3	PR	PD	240	CR	CR
17	62	M	Hypopharynx	2	2b	IVA	2	PR	PR	240	CR	CR
18	69	M	Hypopharynx	2	2b	IVA	3	CR	PR	200	CR	CR
19	57	M	Hypopharynx	2	2b	IVA	3	CR	PR	240	CR	CR
20	61	M	Hypopharynx	2	2b	IVA	3	PR	PR	160	CR	CR
21	56	M	Hypopharynx	2	2c	IVA	3	PR	PR	200	CR	CR
22	55	M	Hypopharynx	3	2b	IVA	3	CR	PR	240	CR	CR
23	51	M	Hypopharynx	4a	2b	IVA	3	PR	PR	200	CR	CR
24	69	M	Hypopharynx	4a	2c	IVA	3	PR	PR	200	PR	PR
25	56	M	Hypopharynx	4a	2c	IVA	3	PR	PR	160	CR	CR
26	62	M	Hypopharynx	2	3	IVB	3	PR	SD	80	CR	SD
27	66	M	Hypopharynx	4a	3	IVB	3	PR	PR	200	CR	CR
28	48	F	Hypopharynx	4b	3	IVB	3	PR	PR	200	CR	CR
29	64	M	Larynx	2	2c	IVA	1	CR	PR	240	CR	CR
30	67	M	Larynx	4a	2b	IVA	3	PR	PR	160	CR	CR

DCF docetaxel, cisplatin, and 5-fluorouracil, *ICT* induction chemotherapy, *CRT* chemoradiation

Table 5 Toxicity grade ≧ 3 due to induction chemotherapy

	Grade 3	Grade 4	Total	%Grade3,4
Neutropenia	11	10	21	70
Febrile neutropenia	7		7	23
Thrombocytopenia	1		1	3
Diarrhea	3		3	10
Enterocolitis	1		1	3
Liver dysfunction	3		3	10
Hyponatremia	3		3	10
Hyperkalemia	1		1	3

Table 6 Toxicity grade ≧ 3 due to concurrent weekly cisplatin chemoradiation

	Grade 3	Grade 4	Total	%Grade3,4
Neutropenia	6		6	20
Febrile neutropenia	2		2	7
Anemia	4		4	13
Thrombocytopenia	1		1	3
Mucositis	11		11	37
Dermatitis	4	1	5	17
Hyponatremia	1		1	3

Figure 1