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Concurrent Chemoradiotherapy with Cisplatin and Docetaxel for Advanced Head and Neck Cancer. A Phase I Study

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Abstract. *Background: This phase I study of weekly low-dose administration of cisplatin (CDDP) and docetaxel (DOC) combined with concurrent conventionally fractionated radiotherapy was designed for locoregionally advanced head and neck cancer. Patients and Methods: Twelve patients were treated at varying levels of DOC (level 1: 5 mg/m^2/week, level 2: 7.5 mg/m^2/week, level 3: 10 mg/m^2/week) with CDDP constant at 20 mg/m^2/week in four cohorts of three patients. Radiation was given at 1.8-2.0 Gy/fraction to a total dose of 60-70.2 Gy. Results: Hematological toxicities, except lymphocytopenia, were minimal. Mucosal toxicities, especially grade 3 mucositis, were common. Dose-limiting toxicity was grade 3 pain, although level 3 did not reach a maximum tolerated dose. No grade 4 toxicities were observed. Complete response rate ranged from 33% to 67% in the various dose levels. Conclusion: This concurrent chemoradiotherapy seems to be a promising treatment modality, in which level 3 is the recommended dose for a phase II study.*

Standard treatment of advanced head and neck cancer consists of surgery and postoperative radiotherapy, resulting in significant anatomic, functional and psychological disorders in the surviving patients (1). Accordingly, a therapeutic strategy aimed at organ-preservation as well as disease control, where radiotherapy plays a central role, has a place for treatment of advanced head and neck cancer. Conventional radiotherapy does not yield long-term locoregional control, resulting in a poor survival rate. Repopulation of tumor cells during therapy, tumor hypoxia and resistance to radiotherapy can cause treatment failure after primary radiotherapy (2-4). A number of efforts have been made to improve this situation. Accelerated fractionation irradiation and hyperfractionated irradiation are representative (5). It has been demonstrated that both accelerated fractionation and hyperfractionation conferred considerable benefits on patients with advanced head and neck cancer.

Systemic chemotherapy in conjunction with radiation is an alternative strategy. Induction chemotherapy followed by radiation for advanced head and neck cancer has failed to improve the survival rate, although organ preservation has been successfully achieved to a high degree (6, 7). Despite its widespread use, this strategy has not been proven superior to radiotherapy alone (8). In contrast, concurrent chemoradiotherapy yields an increase in locoregional control, leading to the improvement of survival rate (9, 10). Meta-analyses have demonstrated the efficacy of concurrent chemoradiation over induction chemotherapy followed by radiation in terms of locoregional control and survival rates (11, 12). The concurrent combined modality seems to be superior to both radiotherapy alone and sequential multimodality therapy. Among numerous systemic chemotherapeutic agents employed for concurrent regimens, cisplatin (CDDP), bolus-administered every three weeks during radiotherapy, is the most prevalent. Although the addition of concurrent high-dose, single-agent CDDP to conventional single daily fractionated radiation has significantly improved survival, it also has increased toxicities, notably hematological and mucosal, which has limited the ability to deliver full doses of radiation or chemotherapeutic agents (13). Accordingly, a new regimen of concurrent chemoradiotherapy is sought, which will overcome the disadvantage of concurrent chemoradiotherapy with high-dose CDDP, while maintaining or improving locoregional disease control and survival rates.

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Recently, there has been an increasing interest in the use of docetaxel (DOC) in concurrent combined modality for the treatment of solid malignancies, particularly non-small cell lung carcinoma and head and neck squamous cell carcinoma (14). The rationale for integrating DOC into combined treatment regimens is based on the efficacy of DOC as a cytotoxic treatment for these classes of tumors (15). More importantly, extensive data has shown its beneficial effect as a radiation sensitizer (16, 17). We combined the radiosensitizing effect of DOC with that of CDDP in an attempt to develop a concurrent chemoradiotherapeutic regimen for advanced head and neck cancer, which would offer equivalent locoregional control and survival rates, as well as decreased toxicity, as compared with concurrent chemoradiotherapy with high-dose CDDP. In this phase I study, weekly administration of low-dose CDDP and DOC was combined with concurrent conventionally fractionated radiotherapy for previously untreated patients with locally advanced head and neck cancer. Dose escalation of DOC was performed to determine the dose-limiting toxicity (DLT) and maximum tolerated dose (MTD), as well as the recommended dose for a phase II study.

Patients and Methods

Patient population. The protocol used was approved by the Institutional Review Board, and all patients went through an informed consent process prior to entry into the trial. Patients were eligible if they met the following criteria: histologically confirmed head and neck cancer, except for one unknown primary cancer and one parotid cancer which were cytologically diagnosed by fine-needle aspiration; stage III or IV disease without evidence of distant metastases; no tumor-specific pretreatment; between the ages of 20 and 75 years old; Eastern Cooperative Oncology Group (ECOG) performance status ≤1; and no major impairment of liver, kidney, or bone marrow, fulfilling the condition of AST/ALT <2 times the upper limit of normal (ULN), serum creatinine <1.5mg/dl, creatinine clearance >60ml/min, white blood cell count >4000/mm^3, neutrophil count >2000/mm^3 and platelet count >100,000/mm^3. Both active infection and major heart or lung disorders were considered as contraindications. Patients who were pregnant or had uncontrolled diabetes mellitus were excluded from the study.

Staging procedures consisted of careful physical examination, endoscopy, chest X-ray, computed tomography and magnetic resonance imaging of the head and neck. Computed tomography and magnetic resonance imaging were repeated 4 weeks after treatment was completed to help assess the response to treatment. The extent of the disease was defined according to the 2002 International Union Against Cancer TNM classification (UICC 2002).

Radiotherapy. Radiotherapy was given to the primary and neck regions once a day at 4 MV photons with a pair of bilaterally opposed fields for the upper neck and by an anterior port for the lower neck. Thirty fractions of 2 Gy each to a total dose of 60 Gy and 39 fractions of 1.8 Gy each to a total dose of 70.2 Gy were administered at 5 fractions per week to non-nasopharyngeal cancer and nasopharyngeal cancer, respectively. The spinal cord was excluded at 40 Gy. After 40 Gy, the clinical target volume was reduced to encompass only the primary region and the involved neck nodes with a 1-cm margin. Radiotherapy was interrupted if the following toxicities occurred: grade 4 hematological toxicity (leukocytopenia, neutropenia, or thrombocytopenia); any non-hematological toxicity of grade 3 or more (other than mucositis, dysphagia, nausea, vomiting, anorexia, dermatitis, fatigue, or fever); grade 4 mucositis, dysphagia, vomiting, anorexia, dermatitis, or fatigue; grade 1 or more fever. Radiotherapy was restarted after the aforementioned toxicity was resolved. Radiotherapy was also interrupted when physicians judged it adequate, even though the toxicity did not fulfill the criteria of interruption.

Chemotherapy. Patients received chemotherapy on a weekly basis, starting on day 1. Dexamethasone 8mg and famotidine 20mg in 100 ml 0.9% sodium chloride was given as a 1-h infusion, followed by DOC 5, 7.5, or 10 mg/m^2 in 250 ml 5% glucose for 1 h. Subsequently, patients underwent intravenous antiemetic therapy with a 5-HT$_3$ antagonist in 100 ml 0.9% sodium chloride for 1 h, followed by CDDP 20 mg/m^2 in 500 ml 0.9% sodium chloride for 2 h. Post-CDDP hydration consisted of 1,000 ml 5% glucose for 4 h. Patients were subjected to irradiation immediately after the completion of CDDP administration. Grade 3 or more hematological toxicity (leukocytopenia, neutropenia, or thrombocytopenia), grade 1 or more fever, serum creatinine ≥1.5mg/dl, creatinine clearance <50ml/min, or AST/ALT ≥2 times the ULN, led to the interruption of chemotherapy until recovery. Failure to resolve these toxicities for more than one week after chemotherapy was interrupted would result in suspension of subsequent cycles.

Toxicity assessment and dose escalation. Toxicity was evaluated twice a week during treatment according to the 1998 edition of the National Cancer Institute common toxicity criteria (version 2.0). The DLT was defined as follows: grade 4 hematological toxicity (leukocytopenia, neutropenia, or thrombocytopenia); any non-hematological toxicity of grade 3 or more (other than mucositis, dysphagia, nausea, vomiting, anorexia, dermatitis, or fatigue); grade 4 mucositis, dysphagia, vomiting, anorexia, dermatitis, or fatigue; grade 3 mucositis, dysphagia, nausea, vomiting, anorexia, dermatitis, or fatigue, requiring more than one week of interruption of treatment; suspension of two or more cycles of chemotherapy.

The initial dose of DOC was level 1 (5 mg/m^2/week) and was increased by 2.5 mg/m^2/week to a maximum of 10 mg/m^2/week (level 2: 7.5 mg/m^2/week, level 3: 10 mg/m^2/week). The dose of CDDP was maintained at 20 mg/m^2/week. Each level was initially examined in a cohort of three patients. If a DLT was encountered in none or one out of three patients in a cohort, the subsequent group was treated at the next higher dose level. If two out of three patients developed a DLT, another cohort of three patients was added at the same dose level. If two or three out of six patients developed a DLT, the subsequent group was treated at the next higher dose level. If four or more out of six patients developed a DLT, further escalation would be halted and that dose level was declared as the MTD. If three out of three patients in a cohort developed a DLT, further escalation would be halted and that dose level was declared as the MTD. No further dose escalation was carried out even if the MTD was not encountered at level 3. The

Table I. *Patient characteristics (n=12).*

Characteristic	No. of patients (%)			
Sex				
Male	11 (92%)			
Female	1 (8%)			
Age, years				
Median	61			
Range	49-71			
Performance status				
0	6 (50%)			
1	6 (50%)			
Histology				
Squamous cell ca	10 (83%)			
Undifferentiated ca.	2 (17%)			
Primary site				
Nasopharynx	3 (25%)			
Oropharynx	4 (33%)			
Hypopharynx	2 (17%)			
Larynx	1 (8%)			
Parotid	1 (8%)			
Unknown	1 (8%)			
Stage				
III	4 (33%)			
IV	8 (67%)			
TN classification				
	N0	N1	N2	N3
TX	0	0	1	0
T1	0	0	0	1
T2	0	4	1	1
T3	0	0	1	0
T4	0	0	3	0

recommended phase II dose level was defined as that which was one level lower than the declared MTD. If the MTD was not encountered at level 3, this level was recommended for the phase II study.

Results

Twelve patients were enrolled in the present study. Patient characteristics are summarized in Table I. Except for three patients with nasopharyngeal cancer, four patients had an unresectable disease due to either an encasement of the carotid artery by a metastatic node (one oropharyngeal cancer, one hypopharyngeal cancer and one unkown primary cancer) or an extensive tumor embolous in the internal jugular/subclavian vein (one parotid cancer). At level 1, one out of three patients in a cohort developed a DLT, while at level 2, none of the three patients in a cohort developed a DLT. At level 3, two out of three patients in the first cohort developed a DLT, which led to the addition of a second cohort of three patients. Therefore, a total of six patients were treated at level 3. None of the three patients in the second cohort at level 3 developed a DLT.

Hematological toxicity. Table II depicts the hematological toxicity observed according to the dose level. Leukocytopenia, neutropenia, thrombocytopenia, as well as anemia, were minimal throughout the dose levels. Only one patient treated at level 3 presented with grade 3 leukocytopenia. No support with granulocyte colony-stimulating factor (G-CSF) for myelosuppression was necessary. In sharp contrast, lymphocytes were severely affected. All (100%) of the three patients at level 2 and five (83%) out of six patients at level 3 developed grade 3 lymphocytopenia. Nevertheless, no outbreak of interstitial pneumonia was observed. There was no grade 4 hematological toxicity and, in turn, no hematological DLT occurred.

Non-hematological toxicity. As shown in Table III, the most common non-hematological toxicity was mucositis, followed by dysphagia and pain. One (33%) out of three patients at level 2 and four (67%) out of six patients at level 3 developed grade 3 mucositis. One (33%) out of three patients at level 1 and two (33%) out of six patients at level 3, suffering from grade 3 dysphagia, underwent intravenous nutrition. Grade 3 pain, which was compatible to a DLT, affected one (33%) out of three patients at level 1 and two (33%) out of six patients at level 3, indicating that level 3 did not reach the MTD. No other DLT was observed. Both dermatitis and fatigue of grade 3 seemed less frequent even at level 3 (17%). No patient experienced grade 3 or more nausea/vomiting. Toxicities related to the liver and kidney were minimal. Additionally, it should be noted that neither neurological nor pulmonary toxicity was observed. There was no case in which non-hematological toxicity caused a treatment delay of more than one week. No grade 4 non-hematological toxicity was observed, and no patients died of treatment-related toxicity. Accordingly, the recommended phase II dose level was determined to be level 3.

No serious late toxicities, such as osteoradionecrosis, laryngeal necrosis, severe fibrosis, or myelopathy/plexopathy, were observed. Grade 2 mouth dryness, grade 2 dysgeusia and grade 2 laryngeal edema were encountered in six, three and one patients, respectively.

Response. As summarized in Table IV, seven (58%) and two (17%) out of twelve patients had a complete response (CR) and partial response (PR), respectively. Three (25%) patients had a stable disease (SD). No patient with a progressive disease (PD) was observed. Among four patients with non-nasopharyngeal unresectable disease, two (50%) had CR, one (25%) had PR and one (25%) had SD. At level 3, which was defined to be the recommended dose level for a phase II study, CR and PR rates were 67% and 16%, respectively.

Currently, the median follow-up time for all twelve patients is 16 months (9 to 24 months). One out of seven

Table II. *Hematological toxicity.*

	level 1 (n=3)					level 2 (n=3)					level 3 (n=6)				
Toxicity Grade	1	2	3	4	% 3/4	1	2	3	4	% 3/4	1	2	3	4	% 3/4
Leukocytopenia	0	0	0	0	0	1	2	0	0	0	0	2	1	0	17
Neutropenia	0	0	0	0	0	2	0	0	0	0	1	1	0	0	0
Lymphocytopenia	0	2	1	0	33	0	0	3	0	100	0	1	5	0	83
Thrombocytopenia	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Anemia	2	1	0	0	0	2	1	0	0	0	3	2	0	0	0

Table III. *Non-hematological toxicity.*

	level 1 (n=3)					level 2 (n=3)					level 3 (n=6)				
Toxicity Grade	1	2	3	4	% 3/4	1	2	3	4	% 3/4	1	2	3	4	% 3/4
Mucositis	1	1	0	0	0	0	2	1	0	33	1	1	4	0	67
Dysphagia	0	0	1	0	33	2	1	0	0	0	0	4	2	0	33
Pain	0	0	1	0	33	2	1	0	0	0	1	3	2	0	33
Dermatitis	0	1	0	0	0	2	0	1	0	33	2	3	1	0	17
Fatigue	1	1	0	0	0	2	0	0	0	0	2	3	1	0	17
Vomiting	1	0	0	0	0	0	0	0	0	0	1	1	0	0	0
Liver enzyme	2	0	0	0	0	1	0	0	0	0	1	0	0	0	0
Creatinine	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0

patients who had achieved CR relapsed locally and was surgically salvaged. Among the two patients who had achieved PR, one with nasopharyngeal cancer died of disease, while the other one with unknown primary cancer underwent surgical salvage. Among the three patients who had yielded SD, one with parotid cancer died of disease, while two with nasopharyngeal cancer showed no progression of disease. Eight out of twelve patients are alive without evidence of disease, and two are alive with evidence of disease.

Discussion

Chemotherapy in conjunction with radiotherapy, whether concurrent or sequential, has been historically employed for unresectable squamous head and neck cancer to improve its poor prognosis. From 1982 to 1987, the Head and Neck Intergroup conducted a phase III randomized trial comparing radiation therapy alone to radiation and concurrent weekly CDDP given at a dose of 20 mg/m^2/week. Although the response rate was greater in patients treated with the concurrent regimen, the survival rate was only 13 months. Also, it did not differ between the two treatment arms. This study was considered to be a negative trial, and therefore the concurrent weekly CDDP chemo-radiotherapeutic regimen was not adopted as a treatment standard (18). In 1987, the Radiation Therapy Oncology Group (RTOG) reported results from a phase II trial testing radiation and concurrent high-dose CDDP (100 mg/m^2 given every 3 weeks during radiation therapy). CR and 4-year survival rates were 71% and 34%, respectively (19). This study, which yielded a promising result, has formed the clinical basis for the development of a second generation chemoradiotherapeutic regimen with concurrent bolus CDDP. In 2003, the Head and Neck Intergroup reported that radiotherapy in conjunction with concurrent high-dose CDDP improved the survival rate of patients with unresectable squamous head and neck cancer, although it increased toxicity (13). Concurrent chemoradiotherapy has also been recently adopted for locally-advanced resectable as well as unresectable head and neck cancer (10, 20) because deforming surgery followed by postoperative radiotherapy, a standard treatment modality for locally-advanced resectable head and neck cancer, causes a significant decline in the quality of life for the surviving patients. Therefore, concurrent chemoradiotherapy has a place as a substitute for the surgical modality. Given this knowledge, we sought to develop a new chemoradiotherapeutic regimen, not only with equivalent disease control and survival rate, but also with less toxicity, as compared to the regimen with high-dose CDDP.

We employed weekly low-dose administration of chemotherapeutic agents for the purpose of lower

Table IV. *Response to treatment.*

Response	CR	PR	SD	PD	% CR+PR	% CR
Level 1 (n=3)	1	1	1	0	67	33
Level 2 (n=3)	2	0	1	0	67	67
Level 3 (n=6)	4	1	1	0	83	67
Total (n=12)	7	2	3	0	75	58

treatment-related toxicity. DOC was added to CDDP to improve disease control by single agent CDDP when concurrently used in a weekly low-dose fashion (18). DOC is a novel semisynthetic drug of the taxoid class that acts by enhancing tubulin polymerization (21). DOC enhances the effect of radiotherapy by causing cell synchronization at the most radiosensitive phase of the cell cycle (G2/M). CDDP enhances radiosensitivity through the inhibition of DNA repair. The mechanisms by which CDDP and DOC serve as either a cytotoxic agent or radiosensitizer are distinct from each other. Furthermore, *in vitro* data demonstrates not only that cell lines with acquired resistance to CDDP are still sensitive to DOC (22), but also that DOC enhances the cytotoxicity of CDDP by modification of intracellular platinum metabolism (23). Sequence dependency of the agents exists because DOC followed by CDDP shows a stronger antitumor effect than CDDP followed by DOC (23). Therefore, it is likely that CDDP/DOC in combination will confer a synergistic effect on radiation-induced cytotoxicity.

In the present phase I study, the dose of DOC was increased from 5 mg/m^2/week to 10 mg/m^2/week by 2.5 mg/m^2/week increments. The dose of CDDP was fixed at 20 mg/m^2/week, because it has been reported that the cytotoxic effect of CDDP reaches a plateau at a level over 25 mg/m^2/week (24). A couple of phase I studies of weekly administration of single agent DOC with concurrent radiotherapy for head and neck cancer have been reported. Hesse *et al*. observed severe toxicities causing DLTs at an initial dose of 15 mg/m^2/week, and failed to escalate the dose level (25). Suzuki *et al*. reported the MTD and recommended dose of DOC to be 20 and 15 mg/m^2/week, respectively (26). These findings prompted us to set the maximum dose level of DOC at 10 mg/m^2/week, taking into account that DOC was adjunct to CDDP. It is highly probable that severe treatment-related toxicities resulting in DLTs would have been frequently observed at a dose level one higher than level 3, although level 3 did not yield the MTD in the present study.

Hematolgical toxicities observed were minimal, although lymphocytopenia was common in the present chemoradiotherapeutic regimen. It should be emphasized that the present regimen, even at level 3, yielded no myelosuppression requiring support by G-CSF. The use of G-CSF is limited to the minimum requirements because a considerable portion of head and neck cancers express G-CSF receptors on the cell surface. The expression of G-CSF receptors correlates with a reduced survival rate of head and neck cancer patients (27). Moreover, it has been shown that G-CSF enhances the malignant potential of head and neck cancer cells (28). It is also noteworthy that no outbreak of interstitial pneumonia, a rare and potentially fatal complication of DOC treatment, was observed. On the other hand, grade 3 non-hematological toxicities, especially mucosal, were commonly observed. No grade 4 non-hematological toxicity was encountered. At level 3, four (67%) and two (33%) out of six patients developed grade 3 mucositis and dysphagia, respectively. Grade 3 pain, constituting a DLT, was also observed in two (33%) out of six patients at level 3. Low-dose morphine succeeded in the short-term grade-reduction of pain. All toxicities were tolerable and did not require a delay of treatment for more than one week. It is evident that treatment-related toxicities, especially hematological, are significantly reduced in the present chemoradiotherapy with weekly low-dose CDDP and DOC, as compared to that with high-dose CDDP.

The CR rate at level 3 was 67%. This was as high as that of the chemoradiotherapy with bolus CDDP for locoregionally advanced head and neck cancer reported by Vokes *et al.* (20). Moreover, the CR rate for unresectable diseases was 50%. This was also equivalent to that of the chemoradiotherapy with bolus CDDP reported by the Head and Neck Intergroup (13), which varied from 40.2% to 49.4%, depending on the regimen. Of interest is that two of the three non-responders to the present chemoradiothrapy were patients with nasopharyngeal cancer, which generally shows good radiosensitivity. It should be noted, however, that both of them are still alive with progression-free disease for 23 and 14 months, respectively. One of the two partial responders was again a patient with nasopharyngeal cancer, who died of disease in 10 months. None of the three patients with nasopharyngeal cancer enrolled in the present study had complete response.

In conclusion, weekly low-dose administration of CDDP and DOC combined with conventionally fractionated radiotherapy yields locoregional control with fewer toxicities, equivalent to the chemoradiotherapy with bolus CDDP. This chemoradiotherapeutic regimen serves as a primary treatment modality for locoregionally advanced head and neck cancer. Level 3 has been chosen as the recommended dose level and a phase II study is now in progress, which will disclose the efficacy of this chemoradiotherapeutic regimen.

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