

Comparison of standard-dose 3-weekly cisplatin and low-dose weekly cisplatin for concurrent chemoradiation of patients with locally advanced head and neck squamous cell cancer

A multicenter retrospective analysis

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Abstract

Standard treatment for locally advanced (stage III-IV) head and neck squamous cell cancer (LA-HNSCC) is concurrent chemoradiation therapy (CCRT) with cisplatin 100 mg/m² every 3 weeks. For medically unfit patients susceptible to treatment-related adverse events, low-dose weekly cisplatin (30–40 mg/m²) can be used as an alternative. In this study, we retrospectively compared the therapeutic outcomes of low-dose weekly cisplatin regimen and standard regimen in CCRT for LA-HNSCC.

The medical records of histologically confirmed LA-HNSCC patients were retrospectively reviewed from January 1, 2007 to December 31, 2012. Patients who were treated with CCRT as initial treatment were included.

Among 220 patients eligible, 65 (29.5%) were treated with cisplatin dosing schedule of 100 mg/m² every 3 weeks and 155 (70.5%) with 30 to 40 mg/m² weekly. The overall response rate in 3-weekly group was 92.3% and did not differ from that in weekly group (91.0%). The median progression-free survival of the weekly group was not attained but was not significantly different from that of 3-weekly group (50.7 months, 95% confidence interval [CI] 42.2–59.1 months) ($P = .81$). Also, the median overall survival did not differ significantly between 2 groups ($P = .34$).

In the present study, low-dose weekly cisplatin showed therapeutic outcomes comparable to standard-dose cisplatin in CCRT for LA-HNSCC. Prospective comparison of standard-dose three-weekly and low-dose weekly cisplatin is warranted.

Abbreviations: AJCC = American Joint Committee on Cancer, CCRT = concurrent chemoradiation therapy, CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, LA-HNSCC = locally advanced head and neck squamous cell cancer, OS = overall survival, PFS = progression-free survival.

Keywords: chemoradiation, cisplatin, head and neck cancer, toxicity

1. Introduction

Concurrent chemoradiation (CCRT) has become the standard treatment option for locally advanced (stage III-IVB) head and neck squamous cell cancer (LA-HNSCC), since several randomized trials reported a significant survival benefit of adding

chemotherapy to radiation over radiation therapy alone.^[1–4] Also, CCRT enables preservation of organs in neck and improves functional outcomes and quality of life of survivors without compromising survival outcomes, compared to primary surgical approach.^[5,6] The current standard CCRT protocol, based on

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evidences, includes the use of radiation treatment concurrent with 3 cycles of bolus cisplatin 100 mg/m² given in every 3 weeks. Despite improved outcomes with such protocol, treatment-related toxicity continues to be a major concern.^[7] Specifically, adding bolus cisplatin to radiation was associated with increased acute toxicity, including gastrointestinal symptoms (xerostomia, mucositis, and nausea/vomiting), hematologic toxicities, and acute kidney injury.^[8,9] In a randomized trial, more than 70 percent of patients receiving CCRT exhibited grade 3 or higher adverse events with the current standard regimen.^[2] Unacceptable toxicity frequently results in inevitable delay in the delivery schedule of definitive radiation therapy, which in turn might affect overall therapeutic outcome negatively, especially in medically unfit or elderly patients.

To mitigate the treatment-related toxicity following CCRT with standard dosing schedule of cisplatin, several studies have reported the outcomes of various CCRT protocols adopting alternative dosing schedules of cisplatin. Most of them utilized 30 to 40 mg/m² cisplatin given weekly during the whole course of radiation therapy. In a prospective trial performed in stage II-IV nasopharyngeal and oropharyngeal carcinoma, CCRT with weekly 40 mg/m² cisplatin resulted in complete response rate of 80.5% with acceptable toxicity profile.^[10] Recently, results of a meta-analysis of several retrospective studies and 2 small prospective randomized trials comparing weekly cisplatin and 3 weekly cisplatin were reported.^[11] In the study, including 779 patients, there was no significant difference in overall survival between 2 cisplatin dosing schedule, while the group receiving weekly cisplatin was associated with less gastrointestinal toxicities but mucositis of grade 3 or higher.^[11] Since the meta-analysis was performed mainly based on relatively small-sized heterogeneous retrospective reports, however, the results should be validated further in a larger patient cohort or in a well-designed randomized trial.

In the present study, we performed a multicenter retrospective analysis of a large cohort containing patients with LA-HNSCC treated homogeneously and compared the treatment outcomes between 2 cisplatin dosing schedule (ie, 100 mg/m² 3-weekly vs 30–40 mg/m² weekly).

2. Materials and methods

2.1. Study population

The medical records of patients treated at 9 institutions in the Republic of Korea between January 2007 and December 2012 who were histologically diagnosed with head and neck squamous cell carcinoma were reviewed (participating institutions: Chungnam National University Hospital, Chosun University Hospital, Seoul National University Hospital, Chonbuk National University Hospital, Chonnam National University Hwasoon Hospital, Wonkwang University Hospital, Keimyung University Dongsan Medical Center, Chungbuk National University Hospital, and Daejeon Eulji Medical Center). For baseline staging workup, all subjects were evaluated using positron emission tomography of the whole body in addition to contrast-enhanced CT of the neck. In selected cases, magnetic resonance image of the neck was performed for more detailed locoregional staging evaluation. Tumor stage was determined, based on the American Joint Committee on Cancer (AJCC) system (7th edition).

To be eligible for the present study, patients were required to have pathologically proven squamous cell carcinoma of the head and neck; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; major organ (liver, kidney, and bone marrow) function within normal range; and an age of 20 years or

older. All patients included in this analysis were initially treated with upfront concurrent chemoradiation therapy using cisplatin dosing schedule of either 100 mg/m² every 3 weeks or 30 to 40 mg/m² weekly, based on the protocol used in previous studies.^[12,13] A patient was excluded if she/he had any history of a prior malignancy and/or any documented distant metastatic disease.

This research protocol was reviewed and approved by the Institutional Review Boards of all participating institutions.

2.2. Definition of outcomes

Tumor response following the primary concurrent chemoradiation treatment was assessed using the RECIST 1.1 criteria. Progression-free survival (PFS) was defined as the time from the date of commencement of treatment to tumor recurrence, the date of salvage surgery to treat recurrent/persistent disease at any site or any mortality. Overall survival (OS) was calculated as the time from the first day of treatment to death from any cause.

2.3. Statistical analysis

Statistical analysis was performed using SPSS version 18.0 (SPSS Inc., Chicago, IL). All tests used to explore statistical significance were 2-sided, and $P < .05$ was considered statistically significant. Discrete variables were compared using the χ^2 test and continuous variables using the t -test. Survival was assessed using the Kaplan-Meier method, and categorical variables were compared using the log-rank test. For univariate analysis, we selected factors known to impact treatment outcomes, as well as patient and treatment characteristics that differed between 2 cisplatin dosing schedule groups.

3. Results

3.1. Population and tumor characteristics

Of all patients screened, 220 met the eligibility criteria, of whom 65 (29.5%) were treated with cisplatin dosing schedule of 100 mg/m² every 3 weeks and 155 (70.5%) with cisplatin dosing schedule of 30 to 40 mg/m² weekly. The 2 groups did not differ significantly in baseline demographic and clinical characteristics, as shown in Table 1. Demographic data were well balanced between 2 groups, while approximately 20% of patients in both groups were 70 years or older (17.0% in 3-weekly group and 20.6% in weekly group). The performance status of patients of both groups was relatively well-preserved. In terms of tumor characteristics, nasopharynx was the most prevailing primary tumor site (38.5% in 3-weekly group and 42.6% in weekly group).

Cumulative dose of cisplatin given during the course of chemoradiation was comparable between 2 groups. Also, neither total radiation dose delivered nor duration of treatment was significantly different between 2 groups.

3.2. Tumor responses

Following the primary chemoradiation therapy, overall response rate was evaluable in 99.1% of patients. The overall response rate in 3-weekly group was 92.3% and did not differ from that in weekly group (91.0%), as shown in Table 2.

3.3. Survival outcomes

First, we explored whether PFS and OS differed between the 2 groups. The median PFS of the weekly group was not attained

Table 1**Baseline demographic and clinical characteristics.**

	Total (n=220)	Cisplatin dosing schedule		P
		100 mg/m ² every 3 weeks (n=65)	30–40 mg/m ² weekly (n=155)	
Males	183 (83.2%)	57 (87.7%)	126 (81.3%)	0.247
Age at diagnosis, ys				
Mean ± SD		57.4 ± 11.7	58.6 ± 12.0	0.636
Range		22–74	26–84	
ECOG PS				
0	38 (17.3%)	7 (10.8%)	31 (2.0%)	0.525
1	166 (75.5%)	53 (81.5%)	113 (72.9%)	
2	16 (7.2%)	5 (7.7%)	11 (7.1%)	
Location of the primary tumor				
Nasopharynx	91 (41.4%)	25 (38.5%)	66 (42.6%)	0.071
Paranasal sinus	22 (10.0%)	9 (13.8%)	13 (8.4%)	
Oropharynx and oral cavity	52 (24.1%)	10 (15.4%)	43 (27.7%)	
Hypopharynx	24 (10.9%)	6 (9.2%)	18 (11.6%)	
Larynx	31 (12.3%)	13 (20.0%)	14 (9.0%)	
Salivary gland	3 (1.3%)	2 (3.1%)	1 (0.7%)	
Stage				
III	93 (42.3%)	21 (32.3%)	72 (46.8%)	0.100
IVA	92 (41.8%)	34 (52.3%)	58 (37.4%)	
IV B	35 (15.9%)	10 (15.4%)	25 (16.1%)	
Cumulative dose of cisplatin				
> 200 mg/m ²		50 (76.9%)	116 (74.8%)	0.743
≤ 200 mg/m ²		15 (23.1%)	39 (25.2%)	
Total radiation dose, Gy				
Mean ± SD		66.4 ± 4.6	68.4 ± 5.6	0.153
Duration of treatment, ds				
Mean ± SD		39.0 ± 2.6	38.4 ± 2.6	0.892
Median, range		39, 35–44	38, 35–44	

ECOG = Eastern Cooperative Oncology Group, PS = performance status, SD = standard deviation.

at the time of analysis but was not significantly different from that of 3-weekly group (50.7 months, 95% confidence interval [CI] 42.2–59.1 months) ($P = .81$; Fig. 1). The 3-year PFS was not also significantly different between 3-weekly group (64.0%, 95% CI 57.9–70.1%) and weekly group (60.3%, 95% CI 55.6–65.0%). Although the median OS was not attained, the outcome did not differ in both group ($P = .34$; Fig. 2) and the 3-year OS was not also significantly different between 3-weekly group (81.2%, 95% CI 76.0–86.4%) and weekly group (67.4%, 95% CI 63.2–71.6%).

3.4. Influence of cisplatin dosing schedule on the survival of specific subpopulations

Next, we explored whether the similarity in survival outcomes between 2 distinct dose regimens of cisplatin is evident in specific subpopulations. Theoretically, therapeutic approach containing

less intensive chemotherapeutic agents may be of benefit especially to those who are medically unfit or have comorbid conditions, since it is associated with the lower probability of treatment-related complications. Among 43 subjects of 70 years or older (11 in 3-weekly and 32 in weekly), the median PFS of the weekly group was 54.2 months (95% CI 35.6–72.9 months) and was not inferior to that of the 3-weekly group (33.0 months, 95% CI 24.3–41.7 months) ($P = .60$). Also, median OS of the weekly group was 58.3 months (95% CI 40.6–76.0 months) and was not significantly different from that of the 3-weekly group (42.1 months, 95% CI 28.6–55.6 months) ($P = .68$).

4. Discussion

In the present retrospective study, we found that there was no significant difference in treatment outcomes between 2 cisplatin dosing regimens (100 mg/m² every 3 weeks vs 30–40 mg/m²

Table 2**Tumor response following primary concurrent chemoradiation.**

	Total (n=220)	Cisplatin dosing schedule		P
		100 mg/m ² every 3 weeks (n=65)	30–40 mg/m ² weekly (n=155)	
Complete response	123 (56.7%)	37 (57.8%)	86 (55.5%)	
Partial response	78 (35.9%)	23 (35.9%)	55 (35.5%)	
Stable disease	9 (4.0%)	2 (3.1%)	7 (4.5%)	
Progressive disease	5 (2.3%)	1 (1.6%)	4 (2.6%)	
Not assessed	4 (0.9%)	1 (1.6%)	3 (1.9%)	
Overall response rate	201 (92.6%)	60 (92.3%)	141 (91.0%)	0.929

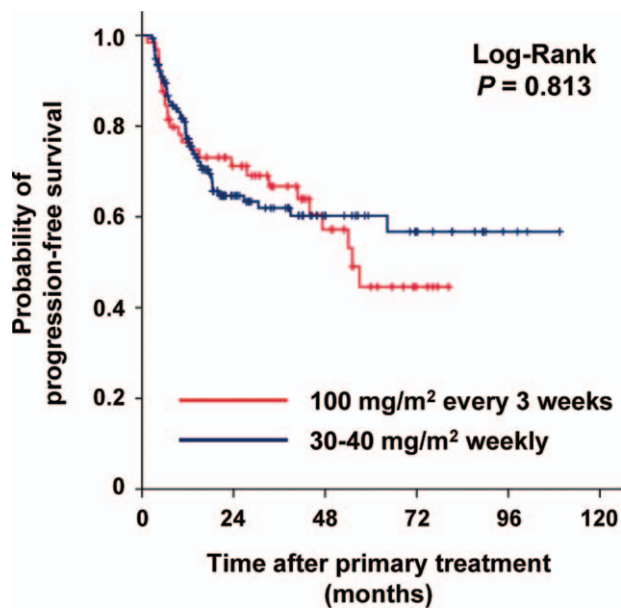


Figure 1. Kaplan-Meier curves showing the estimated progression-free survival according to the dosing schedule of cisplatin during concurrent chemoradiation.

weekly). In addition, the similarity in survival outcomes between 2 distinct dose regimens of cisplatin is also observed in elderly subpopulation. Apart from active tumor control with more intensified treatment, another goal of HNSCC treatment is to minimize treatment-related complications and to maximize functional outcomes.^[14] Especially, for medically unfit patients susceptible to adverse events, alternative therapeutic approach is required to overcome the toxicity of concurrent chemoradiation exploiting standard dose cisplatin (100 g/m² every 3 weeks).^[7-9, 15,16] In previous studies, the frontline concurrent chemo-

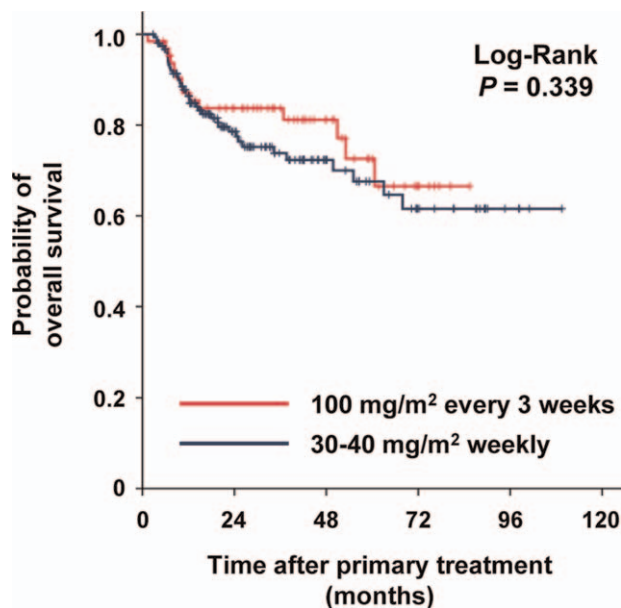


Figure 2. Kaplan-Meier curves showing the estimated overall survival according to the dosing schedule of cisplatin during concurrent chemoradiation.

radiation utilizing weekly regimen of low-dose cisplatin showed fair efficacy and tolerable toxicity profiles.^[17-19] Results of trials performed even in postoperative setting suggested that weekly administration of low-dose cisplatin was acceptable in terms of safety profile.^[20,21] Therefore, in selected patients, the strategy incorporating fractionated administration of low-dose cisplatin might improve compliance to the treatment, maximize dose delivery of cisplatin and eventually prolong the survival of patients with LA-HNSCC.^[22-24]

Alternatively, to alleviate the risk of treatment toxicity, less toxic agents such as cetuximab can be considered as a partner of radiation therapy, since the monoclonal antibody drug showed a positive result in a phase III trial.^[25] In the trial, adding cetuximab to radiation therapy is associated with improved locoregional control and survival without increasing radiation-related toxic events.^[25] However, activity of cetuximab as a component of concurrent chemoradiation therapy still remains elusive, since the evidence from direct comparison of cetuximab and cisplatin is lacking now.

Superiority of a specific cisplatin dosing schedule in the primary concurrent chemoradiation has not yet been studied in well-controlled prospective trial for LA-HNSCC. Recently, results of a meta-analysis comparing weekly cisplatin and 3 weekly cisplatin were reported.^[11] In consistent with our results, there was no significant difference in overall survival between 2 cisplatin dosing schedules,^[11] although it was based only on the analysis of several retrospective series and small-sized prospective studies. While the present study was performed based on the analysis of large population, our study also has potential limitations. In particular, considering the limitation of retrospective review, our results should not be over-interpreted.

Intriguingly, a prospective phase II/III trial comparing 3-weekly and weekly cisplatin for postoperative concurrent chemoradiation therapy is now ongoing in Japan,^[26] planning accrual of 260 patients. Results of such randomized trial of large population will guide the best dosing regimen of cisplatin for concurrent chemoradiation therapy of LA-HNSCC, especially in a specific population.

Taken together, alternative schedule with weekly low-dose cisplatin concurrent with radiation is as effective as 3 weekly standard-dose cisplatin in a large cohort of LA-HNSCC patients. In particular, weekly low-dose cisplatin might be tolerable with improved safety profiles even in medically unfit patients. Prospective comparison of standard-dose 3-weekly and low-dose weekly cisplatin for concurrent chemoradiation therapy of LA-HNSCC patients is warranted.

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