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Original Article

Modified 3-Weekly Cisplatin or Cisplatin-5-Fluorouracil 5-Day Infusion as the Concurrent Chemoradiotherapy Regimen in Locally Advanced Squamous Cell Carcinoma of the Head and Neck: Comparison of Efficacy and Toxicity

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Abstract

Background: Concurrent chemoradiotherapy (CCRT) is an important therapeutic strategy in locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). We evaluated the efficacy and toxicity of two CCRT regimens in treating LA-SCCHN. **Materials and Methods:** LA-SCCHN patients receiving CCRT with either a modified 3-weekly cisplatin 75 mg/m^2 (Group A, $n = 86$) or 5-day continuous infusion of cisplatin 12 mg/m^2 plus 5-fluorouracil (5-FU) 600 mg/m^2 (Group B, $n = 87$) were enrolled. The Kaplan–Meier method was used to estimate overall survival (OS), progression-free survival (PFS), and locoregional recurrence-free survival (LRFS). Univariate and multivariate analyses were performed using Cox proportional hazard models to assess correlations between clinical parameters and survival. **Results:** With a median of 35.8 months' follow-up, the median OS and PFS in Group A and Group B were 65.9 versus 55.0 months ($P = 0.546$) and 34.6 versus 33.3 months ($P = 0.948$), respectively. LRFS was not reached in either group. Group B patients had more Grade 3–4 mucositis (53.7% vs. 32.28%, $P = 0.001$) and dermatitis (49.8% vs. 21.5%, $P = 0.0001$). Trends of higher incidence rates of Grade 3–4 hematologic and renal toxicity were observed in Group A. After statistical adjustment, higher disease stage (Stage IVb) (hazard ratio [HR] = 6.657, 95% confidence interval [CI] 1.786–24.81, $P = 0.005$) and pretreatment anemia (hemoglobin <13 g/dL) (HR = 1.896, 95% CI 1.063–3.391, $P = 0.030$) were associated with poor OS. **Conclusion:** A 5-day cisplatin-5-FU regimen was associated with more frequent Grade 3–4 mucositis and dermatitis than a 3-weekly cisplatin regimen. A multiagent CCRT regimen did not provide survival benefits but increased adverse events.

Keywords: Cisplatin, concurrent chemoradiotherapy, squamous cell carcinoma of the head and neck, toxicity

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Introduction

Concurrent chemoradiotherapy (CCRT) is a cornerstone of treatment for locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN).[1] Concomitant chemotherapy, in combination with radiotherapy (RT), has been reported to provide absolute 5-year survival benefits of 6.5% in both postoperative adjuvant and definitive settings.[2,3] Three-weekly cisplatin 100 mg/m^2 during RT is generally accepted to be the standard regimen worldwide. However, less than two-thirds of patients have been reported to be able to complete the prescribed three cycles of chemotherapy in clinical trials.[4-6] In addition, the significant acute and chronic toxicities caused by CCRT, which compromise the quality of life of patients presenting with SCCHN, are of great concern.[7,8] Different concomitant chemotherapy regimens have been investigated with the goal of improving treatment efficacy and minimizing their toxicity.[9-14] In our previous study, we compared two cisplatin and 5-fluorouracil (5-FU) CCRT regimens and concluded that a higher dose regimen resulted in elevated toxicity despite survival outcomes remaining the same.[15] As a result, we use a lower dose of cisplatin and 5-FU in the routine treatment of SCCHN. On the other hand, we modified the dose of a 3-weekly cisplatin regimen to 75 mg/m^2, which has also been adopted in some Asian countries to enhance tolerability and compliance to CCRT.[16,17] In the present study, we report our experience of using the aforementioned CCRT regimens for patients with LA-SCCHN at a single institution with regards to treatment outcomes and toxicity profiles.

Materials and Methods

Patient eligibility

This retrospective cohort study was approved on Aug-4th 2015 by MacKay Memorial Hospital Institutional Review Board (MMH-IRB) with the approval number 15MMHIS053. Informed consent form from patients was not required in this approved study. Patients presenting with pathologically confirmed, newly diagnosed, nonmetastatic LA-SCCHN (Stage III, IVa, IVb) were enrolled in the study. The primary tumors in all cases arose from the oral cavity, oropharynx, hypopharynx, or larynx. All patients had a detailed history of physical examinations, including fibroscopy and imaging studies such as computed tomography, magnetic resonance imaging, abdominal ultrasonography, and bone scintigraphy. Cancer staging was made according to the American Joint Committee on Cancer 7th edition. Patients receiving either definitive or postoperative adjuvant CCRT were eligible to participate in the study. After completing treatment, regular outpatient follow-up visits were arranged, consisting of monthly visits in the 1st year, visits every 3 months in the following 2 years, and every 6 months thereafter. In the event that the disease recurred, the treatment was provided at the discretion of the treating physician as per clinical conditions after considering the patient's best interests.

Multimodality treatments

The choice of treatment was made after a multidisciplinary team discussion, and the final decision was made by the patient and the treating physician. The patients who received curative surgery underwent local tumor-wide excision and standard unilateral or bilateral neck dissection. All surgically treated patients had R0 resection. Postoperative CCRT was performed for patients presenting with any major pathologic features, including surgical margin or extranodal extensions. Patients with two or more minor pathologic features, including a close surgical margin (1–5 mm), poorly differentiated histology, lymphovascular invasion, perineural invasion, and/or multiple positive lymph nodes (N2b or higher nodal disease) also received adjuvant CCRT at our institution. Induction chemotherapy was performed prior to definitive CCRT, and the regimens included cisplatin and 5-FU with or without docetaxel.

The mode of irradiation used in all patients was intensity-modulated RT. The daily radiation dose was 1.8–2 Gy, and it was delivered in 5 fractions per week. The highest radiation dose was 66 Gy to the primary tumor sites and metastatic lymph nodes, and 60 Gy or 54 Gy to the lower risk areas in postoperative CCRT. In the definitive CCRT setting, the highest dose was 70 Gy, followed by 66 and 60 Gy. CCRT-related toxicity can prolong the RT treatment time and is regarded to be a poor prognostic factor. When completing whole RT treatment took longer than 50 days, it was defined as RT prolongation.

Two chemotherapy regimens were compared. One consisting of 3-weekly cisplatin 75 mg/m^2 delivered on day 1, 22, and 43 during RT (Group A), and the other consisting of cisplatin 12 mg/m^2 and 5-FU 600 mg/m^2 delivered as a continuous infusion for 120 h at week 1 and week 5 during RT (Group B). The patients were adequately hydrated and given the same antiemetic agents, including palonosetron, aprepitant, and dexamethasone. The patients were followed up at the outpatient department weekly during RT. Toxicities were recorded according to the Common Terminology Criteria for Adverse Events version 4.03 and managed appropriately.

End points and statistical analysis

All of the time-related endpoints were counted from the date of the first treatment to the date of the occurrence of events. The data cutoff date was December 31, 2016. Patients who were lost to follow-up and those with no events until the data cut-off date were recorded as being "censored." Two years of follow-up was required for all living patients to be included in the analysis. Any cause of death was accounted for in the overall survival (OS). Events consisting of locoregional or distant recurrence, second primary cancer, disease progression after initial treatment, or any cause of death were accounted for in the progression-free survival (PFS). The events for locoregional recurrence-free survival (LRFS) were primary tumor and/or regional lymph node recurrence or progression. Clinical and pathological characteristics between the two groups were calculated using two-sample *t*-tests or Fisher's exact test. The OS, PFS, and LRFS were analyzed using the Kaplan–Meier method. We also analyzed the clinical parameters including age (<50 vs. ≥50 years), the Eastern Cooperative Oncology Group performance status (0 vs. 1), disease Stage (III vs. IVa vs.

IVb), primary tumor site (oral cavity vs. others), prolonged RT duration (<50 days vs. ≥50 days), pretreatment hemoglobin (Hb) level (<13 vs. ≥13 g/dL), and chemotherapy regimen (3-weekly cisplatin vs. cisplatin/5-FU), factors which may have affected survival outcomes. Univariate and multivariate analyses of these parameters were evaluated using Cox-proportional hazard models. The statistical analyses and preparation of graphs were performed and created using SPSS (version 22) (IBM Corp, Armonk, NY, USA) and SAS (version 9.4) (SAS Institute Inc.,Cary, NC, USA).

Results

Patient characteristics and overall treatment results

From May 2010 to December 2014, a total of 173 patients were included in our analysis. Eighty-six patients received postoperative CCRT, and the others received definitive CCRT. The baseline patient characteristics were balanced between the two chemotherapy groups [Table 1]. At a median follow-up of 35.8 months (interquartile range: 15.1–56.8 months), the median OS of the overall patient population was 65.9 months (95% confidence interval [CI]: 46.2–85.8 months), and the median PFS was 34.6 months (95% CI: 19.6–49.6 months). At the last follow-up date, there were 41 and 42 deaths in Group A and Group B, respectively. The events of PFS in the two groups are shown in Table 2.

Comparison of toxicity profiles

There were two and three CCRT-related deaths in Group A and Group B, respectively. The major Grade 3 and 4 toxicity profiles of the two regimens are summarized in Table 3. Group B had higher incidence rates of Grade 3–4 mucositis (53.7% vs. 32.3%, $P = 0.002$) and dermatitis (49.8% vs. 21.5%, $P = 0.0001$) than Group A. There was a trend of increased Grade 3–4 elevated serum creatinine in Group A (5.8% vs. 1.2%, $P = 0.099$). Nineteen patients in Group A (22.1%; patient refusal: 2; renal function deterioration: 10; neutropenia: 6; and mucositis: 1) and 11 patients in Group B (12.6%; mucositis: 7; dermatitis: 3; and neutropenia: 1) could not complete the defined chemotherapy dosing schedule. One patient in each group could not complete the defined RT dose. Forty patients (46.5%) in Group A and 46 patients (52.9%) in Group B had RT prolongation.

Comparison of the treatment efficacy

The median PFS in Group A was 34.6 months (95% CI: 10.9–58.3 months) compared to 33.3 months (95% CI: 12.4–54.3 months) ($P = 0.948$) Figure 1a in Group B. The median OS was 65.9 months (95% CI: 47.2–84.8 months) in Group A compared to 55 months (95% CI: 33.7–76.3 months) in Group B ($P = 0.546$) [Figure 1b]. The median LRFS was not reached in either group ($P = 0.806$) [Figure 1c]. The estimated 1-year, 2-year, and 3-year PFS, OS, and LRFS rates were not significantly different between the two groups [Table 4]. Univariate analysis of OS showed that in patients with Stage IVb and pretreatment Hb level <13 g/dL, the outcomes were significantly worse. In multivariate analysis, the hazard ratio (HR) of OS was 6.657 (95% CI: 1.786–24.81, $P = 0.005$) for patients with Stage IVb disease and 1.896 (95% CI:

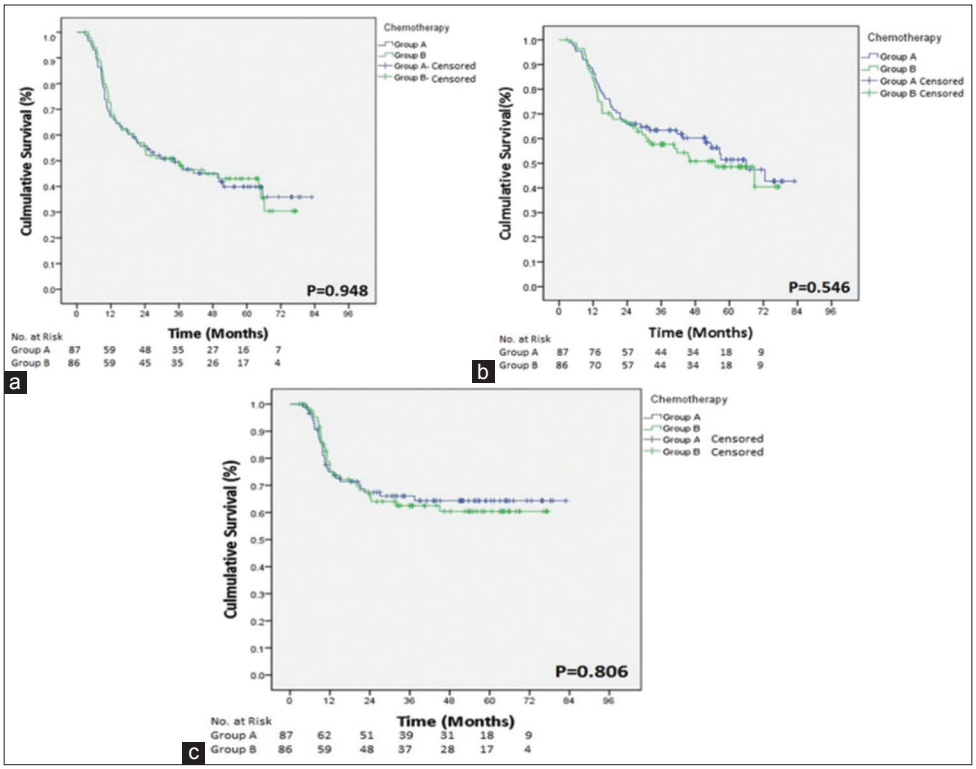

Figure 1: The Kaplan–Meier survival curve of the two chemotherapy regimens. (a) progression-free survival; (b) overall survival; (c) locoregional recurrence-free survival. Group A denotes 3 weekly cisplatin. Group B denotes cisplatin plus 5-fluorouracil. $P < 0.05$ represents statistical significance

Table 1: Clinical and pathologic characteristics of the two concurrent chemoradiotherapy regimen groups

Parameters *n* (%) or median (range)	Postoperative CCRT			Definitive CCRT		
	Group A*	Group B†	*P*‡	Group A*	Group B†	*P*‡
Age (years)	49 (31-68)	50 (32-67)	0.361	54 (41-73)	52 (35-73)	0.173
Sex						
Male	43 (97.7)	37 (88.1)	0.119	42 (97.7)	41 (93.2)	0.317
Female	1 (2.3)	5 (11.9)		1 (2.3)	3 (6.8)	
ECOG						
0	35 (79.6)	32 (76.2)	0.708	35 (81.4)	41 (93.2)	0.098
1	9 (20.4)	10 (23.8)		8 (18.6)	3 (6.8)	
Tumor site						
Oral cavity	38 (86.4)	33 (78.6)	0.622	7 (16.3)	8 (18.2)	0.225
Oropharynx	3 (6.82)	4 (9.5)		19 (44.2)	27 (61.4)	
Hypopharynx	3 (6.82)	5 (11.9)		15 (34.9)	7 (15.9)	
Larynx	0	0		2 (4.7)	3 (4.6)	
Stage						
III	6 (13.6)	7 (16.7)	0.307	10 (23.3)	6 (13.6)	0.222
IVa	37 (84.1)	31 (73.8)		31 (72.1)	32 (72.7)	
IVb	1 (2.3)	4 (9.5)		2 (4.6)	6 (13.6)	
RT dose (Gy)	66 (66-70)	66 (52-70)	0.089	70 (59.4-84.6)	70 (60-70)	0.089
RT duration (days)	48 (45-65)	50 (44-79)	0.141	52 (47-84)	51.5 (36-70)	0.223
Pretreatment hemoglobin (g/dL)	14.6 (7-18.6)	14.1 (8.2-16.9)		14.2 (8.1-17.5)	13.6 (10.0-17.2)	0.90
Surgical margin						
Positive	6 (13.6)	12 (30.0)	0.181			
Close (1-5 mm)	31 (70.5)	22 (55.0)				
Safe (>5 mm)	7 (15.9)	6 (15.0)				
Tumor differentiation						
Well	9 (20.5)	13 (30.9)	0.516			
Moderate	31 (70.5)	25 (59.5)				
Poor	4 (9.1)	4 (9.5)				
Lymphovascular invasion						
No	29 (65.9)	21 (50.0)	0.135			
Yes	15 (34.1)	21 (50.0)				
Perineural invasion						
No	28 (63.6)	23 (56.1)	0.478			
Yes	16 (36.4)	18 (43.9)				
Extracapsular extension						
No	28 (68.3)	27 (64.3)	0.699			
Yes	13 (31.7)	15 (35.7)				

*Group A denotes 3-weekly cisplatin, †Group B denotes cisplatin plus 5-FU, ‡P<0.05 indicates statistical significance. RT: Radiotherapy, CCRT: Concurrent chemoradiotherapy, 5-FU: 5-fluorouracil, ECOG: Eastern Cooperative Oncology Group

Table 2: Progression-free survival events in each chemotherapy group

PFS events	Group A* (*n*)	Group B† (*n*)
Locoregional recurrence or progression	26	30
Distant metastasis	9	7
2nd primary SCCHN‡	8	5
2nd primary non-SCCHN‡	6	5
Non-cancer related death	4	5

*Group A denotes 3-weekly cisplatin, †Group B denotes cisplatin plus 5-FU, ‡SCCHN: Squamous cell carcinoma of the head and neck. SCCHN: Squamous cell carcinoma of the head and neck, PFS: Progression-free survival, 5-FU: 5-fluorouracil

1.063–3.391, $P = 0.003$) for patients with pretreatment Hb level <13 g/dL compared to the reference group [Table 5]. With regards to PFS, the outcome was significantly worse only in the patients with Stage IVb disease in both univariate and multivariate analyses. The HR of PFS was 8.868 (95% CI: 1.784–44.07, $P = 0.008$) for patients with Stage IVb disease compared to the reference group [Table 6]. The choice of chemotherapy regimen did not significantly influence the OS and PFS in this study.

Discussion

It is always a clinical challenge to choose the appropriate chemotherapy regimen in combination with radiation when treating LA-SCCHN patients. Most previous studies comparing different CCRT regimens have been retrospective in nature.[10,18-25] In this retrospective cohort study, we compared

Table 3: Grade 3-4 toxicities of the two chemotherapy regimens

	Group A* (%)	Group B† (%)	*P*‡
Mucositis	32.3	53.7	0.002
Dermatitis	21.2	49.8	<0.0001
Anemia	27.6	19.8	0.227
Neutropenia	13.8	8.1	0.234
Thrombocytopenia	6.9	3.5	0.313
Infection	20.7	19.8	0.880
Vomiting	5.8	4.7	0.745
Elevated serum creatinine	5.8	1.2	0.099

*Group A denotes 3-weekly cisplatin, †Group B denotes cisplatin plus 5-FU, ‡*P*<0.05 indicates statistical significance. 5-FU: 5-fluorouracil

Table 4: 1-year, 2-year and 3-year progression-free survival, overall survival and locoregional recurrence-free survival of the two chemotherapy groups

	Group A* versus B†		
	PFS	OS	LRFS
1-year	67.0% versus 70.2%	87.5% versus 84.5%	75.1% versus 76.2%
2-year	55.6% versus 55.8%	65.9% versus 66.6%	67.4% versus 66.8%
3-year	49.4% versus 49.5%	63.4% versus 57.7%	66.0% versus 62.5%

*Group A denotes 3-weekly cisplatin, †Group B denotes cisplatin plus 5-FU. PFS: Progression-free survival, OS: Overall survival, LRFS: Locoregional recurrence-free survival, 5-FU: 5-fluorouracil

the treatment efficacy and toxicity between two regimens in both definitive and postoperative CCRT settings. Other studies have also included patients with or without upfront surgery; however, they have not detailed the pathologic characteristics, which may affect the treatment outcomes.[10,18,20-23,25] In the current study, the clinical and pathological parameters were well balanced between the two groups. With regards to the toxicity profiles, the rates of Grade 3–4 mucositis and dermatitis were significantly increased in the patients receiving cisplatin/5-FU, which is consistent with previous studies.[10,18,22] However, we found higher incidence rates of chemotherapy-related Grade 3–4 hematologic toxicity [Table 3] and elevated serum creatinine (5.8% vs. 1.2%, $P = 0.099$) in the patients receiving 3-weekly cisplatin. Rades *et al*. demonstrated that multiagent chemotherapy provided no benefits on survival and disease control.[10,18,22] However, the incidence of chemotherapy-related toxicity in our study was not as high as that reported with standard 3-weekly cisplatin 100 mg/m^2 in other reports.[10,18,22] Chemotherapy regimens with higher toxicity profiles can compromise the chemotherapy completion rate and prolong the length of RT treatment[26] both of which can result in inferior treatment outcomes.[10,18,21-23] A relatively high proportion of the patients in Group A (79%) and B (87%) tolerated chemotherapy without dose modification or discontinuation in our study. However, more severe mucositis and dermatitis in Group B (52.9%) led to a longer length of RT treatment than in Group

Table 5: Univariate and multivariate analysis of parameters related to overall survival

Parameters	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P*†	Hazard ratio	95% CI	*P*†
Age						
<50-year-old	Ref.			Ref.		
≥50-year-old	1.156	0.813-1.866	0.319	1.120	0.810-1.894	0.322
ECOG						
0	Ref.					
1	1.177	0.652-2.125	0.588			
Tumor site						
Oral cavity	Ref.					
Oropharynx	1.161	0.724-1.863	0.536			
Hypopharynx	0.884	0.459-1.700	0.711			
Larynx	0.569	0.264-5.106	0.273			
Stage						
III	Ref.			Ref.		
IVa	0.989	0.597-1.637	0.965	0.898	0.531-1.518	0.687
IVb	6.094	1.658-22.40	0.007	6.657	1.786-24.81	0.005
Anemia‡						
N	Ref.			Ref.		
Y	1.794	1.035-3.111	0.037	1.896	1.063-3.391	0.030
RT delay§						
N	Ref.					
Y	0.790	0.514-1.214	0.283			
Chemotherapy						
Group A¦	Ref.			Ref.		
Group B¶	1.238	0.813-1.886	0.319	1.239	0.810-1.896	0.322

†*P* denotes *P* value, *P*<0.05 indicates statistical significance, ‡Anemia: Pretreatment hemoglobin <13 g/Dl, §RT delay: Total radiotherapy treatment duration >50 days, ¦Group A denotes 3-weekly cisplatin, ¶Group B denotes cisplatin plus 5-FU. 95% CI: 95% confidence interval, 5-FU: 5-fluorouracil, RT: Radiotherapy

Table 6: Univariate and multivariate analysis of parameters related to progression-free survival

Parameters	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P*†	Hazard ratio	95% CI	*P*†
Age						
<50 y/o	Ref.			Ref.		
≥50 y/o	1.129	0.705-1.809	0.614	1.263	0.788-2.025	0.332
ECOG						
0	Ref.					
1	0.959	0.490-1.878	0.9.3			
Tumor site						
Oral cavity	Ref.					
Oropharynx	1.071	0.631-1.817	0.801			
Hypopharynx	0.884	0.334-1.873	0.594			
Larynx	0.966	0.664-3.176	0.776			
Stage						
III	Ref.			Ref.		
Iva	0.990	0.563-1.742	0.972	1.027	0.581-1.819	0.926
IVb	8.593	1.745-42.03	0.008	8.868	1.784-44.07	0.008
Anemia‡						
N	Ref.					
Y	1.399	0.730-2.682	0.312			
RT delay§						
N	Ref.					
Y	0.899	0.553-1.462	0.668			
Chemotherapy						
Group A‖	Ref.			Ref.		
Group B¶	1.129	0.705-1.809	0.614	1.157	0.719-1.861	0.549

†*P* denotes *P* value, *P*<0.05 indicates statistical significance, ‡Anemia: Pretreatment hemoglobin <13 g/dL, §RT delay: Total radiotherapy treatment duration >50 days, ‖Group A denotes 3-weekly cisplatin, ¶Group B denotes cisplatin plus 5-FU. 95% CI: 95% confidence interval, FU: 5-fluorouracil, RT: Radiotherapy

A (46.5%). Although a prolonged RT time has been shown to be a poor prognosticator in LA-SCCHN,[26] this factor did not affect the survival outcomes in this study.

The results of efficacy endpoints in this study, which included 1–3-year OS, PFS, and LRFS, were quite similar to other retrospective studies.[10,21-23] No additional survival benefits were observed when multiagent regimens were compared to the single-agent cisplatin in this study and other reports.[10,18,19,22,27] However, it is still debatable as to whether the optimal dosing schedule of single-agent cisplatin acts as a radiosensitizer. Weekly cisplatin 30–40 mg/m^2 and a split dose of cisplatin are the most frequently tested schedules.[21,23,28] High-dose 3-weekly cisplatin may be a less tolerated regimen in head and neck cancer patients, especially in Asian populations. Regimens with weekly cisplatin alone or in combination with 5-FU have commonly been reported in this patient population to improve compliance and treatment efficacy.[29,30] Due to its convenience and less toxicity, weekly cisplatin during CCRT is a frequently used regimen in Taiwan.[31] Despite improved toxicity profiles, weekly cisplatin regimens cannot replace the standard 3-weekly cisplatin regimen from the aspect of treatment efficacy.[32,33] In addition, no previous study has tested a modified 3-weekly cisplatin regimen as used in this study. Apart from the disease stage, we found that lower pretreatment Hb level (<13 g/dL) resulted in inferior survival outcomes in both the univariate and multivariate analyses. The pretreatment anemia has been reported to be a poor prognostic factor in LA-SCCHN patients in several studies.[34-36] Anemia itself can represent an indicator of poor general condition and nutritional status before treatment. Moreover, anemia may contribute to tumor hypoxia and decrease CCRT efficacy.

Although the treatment efficacy and toxicity profile of the two regimens in our study were comparable to those reported in other studies, our results should still be interpreted with caution due to its retrospective nature. In addition, data on the human papillomavirus status of the oropharyngeal tumors (accounting for 30.6% of the overall study population) were not available in this study, although this has been shown to play a significant role in treatment response and survival outcomes.

Conclusion

In summary, we demonstrated that both the modified 3-weekly cisplatin and cisplatin/5-FU regimens were well tolerated and had high treatment completion rates. However, the multiagent regimen did not enhance the treatment outcomes and increased CCRT toxicity. Based on the current evidence, 3-weekly cisplatin treatment should still be the standard regimen of care for patients undergoing CCRT for SCCHN. Further

studies may be warranted to investigate dose modification of 3-weekly cisplatin.

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Conflicts of interest

There are no conflicts of interest.

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