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ORIGINAL ARTICLE

Promising overall survival of patients with recurrent/metastatic squamous cell carcinoma of head and neck receiving gemcitabine plus cisplatin treatment: report of a multi-center phase II study

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Abstract
Purpose The efficacy and safety of gemcitabine in combination with cisplatin (GC) as the first-line treatment in patients with recurrent/metastatic (R/M) squamous cell carcinoma of head and neck (SCCHN) was examined.
Patients and methods Patients with R/M SCCHN without prior treatment for their R/M disease were eligible and treated with gemcitabine 1,250 mg/m^2 on day 1, day 8 and cisplatin 80 mg/m^2 on day 8 every 21 days.
Results Forty patients were enrolled from March 2004 to January 2006, and 30 were evaluable for treatment effectiveness and outcome. The median age of evaluable patients was 50 years and all patients were male. Partial response was observed in 9 (30%) and stable disease in 7 (23.3%) patients. The overall response rate and disease control rate was 30 and 53.3%, respectively. The major toxic effects were ≥grade 3 leukopenia and anemia (65 and 27.5%, respectively). With a follow-up of 72 months, the median time to progression (TTP) was 128 days (95% CI, 78–242) and median overall survival (OS) was 401 days (95% CI, 216 ~not reached).
Conclusions This GC regimen demonstrates a good activity and a promising survival period in patients with R/M SCCHN.

Keywords Squamous cell carcinoma of head and neck · Recurrent · Metastasis · Gemcitabine

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Introduction

Squamous cell carcinoma of head and neck (SCCHN), which includes cancers originated from oral cavity, oropharynx, hypopharynx and larynx, represents the sixth most frequent type of cancer in the world [1]. The increasing incidence and dismal outcome of SCCHN become a major problem of public health in Taiwan. Habitual consumption of betel nuts results in a high prevalence of oral cavity cancer in Taiwan [2]. Furthermore, approximately 70% of SCCHN patients present with locoregional disease at diagnosis, and SCCHN is the fourth most frequent cause of death among male cancer patients in Taiwan [3]. Despite optimization of treatment strategies to primary tumors, more than 60% of patients with advanced disease develop local and/or regional recurrences and approximately 20% present with metastases [4]. The backbone of the treatment for recurrent/metastatic (R/M) disease is cisplatin, and cisplatin combined with 5-fluorouracil (i.e., the CF regimen) is

regarded as the standard regimen for R/M SCCHN [5, 6]. In addition, methotrexate, bleomycin, and other agents have been incorporated into cisplatin-based regimens. However, the prognosis is poor with median survival in the range of 6–9 months irrespective of the regimen used [5–8]. These unacceptably poor results have prompted some investigators to shift their attention to taxanes (paclitaxel and docetaxel) [9–11]. However, no survival benefit was demonstrated in patients treated with paclitaxel/cisplatin in comparison with the CF regimen [11]. Therefore, finding new combination chemotherapies to extend survival in R/M SCCHN cases with acceptable toxicity is of the utmost importance.

Gemcitabine (2′,2′-difluoro-2′-deoxycytidine) is a nucleoside analog with broad anti-solid tumor activity. The activity against SCCHN has been shown: the response rates of gemcitabine as a single agent for R/M SCCHN is modest (0–13%) with a low incidence of hematologic toxicity [12, 13]. Combination of gemcitabine with taxanes (docetaxel, paclitaxel) showed promising results [4, 14]. Preclinical and clinical data show synergistic activity between gemcitabine and cisplatin without overlapping toxicity [15]. However, there are very few reports regarding the activity of gemcitabine combined with cisplatin (the GC regimen) in advanced SCCHN. The efficacy of GC combined with radiotherapy in the treatment of locally advanced SCCHN has been reported [16]. In R/M SCCHN, only Hitt et al. [17] demonstrated an overall response rate of 22.7% without providing documentation of survival data. These results suggest that gemcitabine has substantial activity against SCCHN, and the effectiveness and survival benefit of GC regimens in oriental R/M SCCHN cases deserves further study. To investigate the efficacy and tolerability of the GC regimen in R/M SCCHN, we therefore conducted this multicenter phase II trial.

Patients and methods

Study design

This is an open-label, non-comparative multicenter phase II clinical trial to assess efficacy and safety of treatment with gemcitabine in combination with cisplatin (GC) for patients with R/M SCCHN. The primary objective of the study is to determine the overall response rate (ORR) of GC, and the secondary objective is to evaluate the overall survival (OS), time to progression (TTP), and safety profile. The sample size was calculated based on the two-stage design by Simon [18]. The treatment program was designed to refuse response rates of 10% (P0) and to provide a significance level of 0.05 (α) with a statistical power of 80% ($\beta = 0.2$) in assessing the activity of the regimen as a 30% response rate (P1). Thus, the first step was planned to include 10 patients; if >1 patients' responses were recorded, an additional 19 patients up to a total number of 29 were enrolled. The regimen was considered active if >6 responses were recorded. The approval of the local ethics committee was obtained before the start of the trial.

Patient selection

The criteria for inclusion were: histologically confirmed non-nasopharyngeal SCCHN and written informed consent to participate in the trial; locoregional recurrence and/or metastases after primary curative local treatment and unsuitable for further radiotherapy and surgery; or primary distant metastases at diagnosis; presence of at least one lesion defined as being $\geq$20 mm in at least one dimension measured with conventional computed tomography (CT) or $\geq$10 mm in at least one dimension measured with spiral CT scan or magnetic resonance imaging (MRI); ECOG performance status $\leq$2; age between 20 and 70 years; and life expectancy of at least 12 weeks. Patients who fulfilled any of following criteria were excluded from the trial: previous induction or adjuvant chemotherapy within 3 months; presence of central nervous system (CNS) metastases; other malignancy with the exception of curatively treated non-melanoma skin cancer or cervical carcinoma in situ prior to entry into the study; bone-only metastasis; previous treatment with gemcitabine; white blood cell (WBC) less than 3,500/mm^3, absolute neutrophil count (ANC) less than 1,500/mm^3, or platelets less than 100,000/mm^3; serum bilirubin greater than 1.5 times the upper limit of normal range (ULN); alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 2.5 times the ULN if no demonstrable liver metastases, or greater than 5 times the ULN in the presence of liver metastases; creatinine clearance $\leq$60 ml/min (based upon urine collection); concomitant illness including uncontrolled infection or other active, uncontrolled disease such as congestive heart failure, angina pectoris, respiratory insufficiency, and arrhythmia; documented hypersensitivity to platinum compounds; and women of child-bearing potential (pregnancy or breast feeding).

Treatment plan

All eligible patients received gemcitabine (Gems®, TTY Biopharm, Taipei, Taiwan) at a dose of 1,250 mg/m^2 by intravenous (i.v.) infusion over 30 min on day 1 and day 8, and cisplatin 80 mg/m^2 by i.v. infusion for 4 h on day 8 only, every 21 days, until disease progression, intolerable toxicity, or consent withdrawal. It was recommended that the infusion program contain at least two liters of fluids over a minimum of 4 h. The treatment schema is shown in Fig. 1.

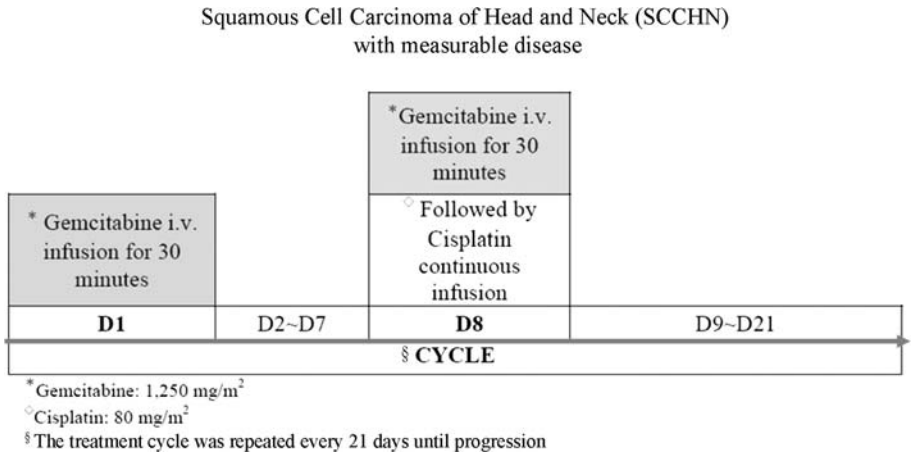

Fig. 1 Treatment schema for the study patients

Dose modification

Dose modification was based on the worst toxicity (graded according to the Common Terminology Criteria for Adverse Events of National Cancer Institute, version 2.0 [19]). If hematological criteria (ANC $\geq$ 1500/mm^3; platelet $\geq 7.5 \times 10^4$/mm^3) needed to begin the day-1 treatment of a cycle were not met, treatment was postponed for a maximum of 2 weeks or until recovery. The dose of both gemcitabine and cisplatin was reduced to 75% on day-8 of administration if the ANC fell into the range 1,000–1,500/mm^3 or the platelet count fell into the range $5.0–7.5 \times 10^4$/mm^3. If the ANC fell below 1,000/mm^3 or the platelet count fell below 5.0×10^4/mm^3, the day-8 administration of both drugs was omitted. If patients suffered from >grade 1 non-hematological toxicity except nausea, vomiting, or alopecia, treatment was withheld for a maximum of 3 weeks to allow the toxicity to resolve or severity to decrease to grade 1. If patients still did not recover from the toxicity (as mentioned above) after 3 weeks delay, they were withdrawn from the study. Estimated creatinine clearance (CcR) was calculated using the Cockroft-Gault formula prior to cisplatin administration. Cisplatin dose was adjusted according to the following: CcR >60 ml/min, full dose of cisplatin; 40–60 ml/min, half-dose of cisplatin; and <40 ml/min, withheld cisplatin. If patients suffered from $\geq$grade 3 neurological toxicities, they were withdrawn from the study.

Efficacy and safety evaluation

Tumor responses were evaluated by RECIST criteria [19]. The primary efficacy variables of this study were the overall response rate (ORR) defined as sum of complete response (CR) and partial response (PR), and disease control rate (DCR) defined as sum of CR, PR and stable disease (SD). Tumor assessment was performed by spiral CT or MRI before the initial treatment and repeated every two cycles until withdrawal from this study. Before a status of CR, PR or SD could be assigned, the tumor measurements were supposed to be confirmed by another scan at least 4 weeks later. Time to progression (TTP) was measured from the date of initiation of study treatment to the date of disease progression, death, or last follow-up. Overall survival (OS) was measured from the date of study treatment initiation to the date of death or last follow-up. Severity of toxicity was reported and graded using Common Terminology Criteria for Adverse Events of National Cancer Institute (NCI-CTCAE), version 2.0 [20]. Toxicity was assessed before treatment and at each visit every week until the end of or withdrawal from the study.

Statistical analysis

All analyses were performed using SPSS version 12.0 software (SPSS, Inc., Chicago, IL, USA). Median and life tables were computed using the product-limit estimate by the Kaplan–Meier method, and the log-rank test was applied for comparison of survival periods between groups. The response analysis of each clinical factor was compared using χ^2 or Fisher's exact test for categorical variables. Two-sided p values less than 0.05 were considered statistically significant.

Results

Patients characteristics

From March 2004 to January 2006, a total of 40 patients (all male; mean age, 51 years; 30 evaluable) from Taipei Veterans General Hospital and Chang-Gung Memorial Hospital Li-Kou Center were enrolled. Among these cases, 10 patients were considered to be not evaluable due to the following reasons: 5 patients received less than 2 cycles of treatment and discontinued due to intolerance (skin rashes

Table 1 Demographics and patient characteristics of the ITT and EP

Characteristics	ITT (%) (n = 40)	EP (%) (n = 30)
Age		
Range	39–65	39–65
Medium	51	50
Gender		
Male	40 (100)	30 (100)
Female	0 (0)	0 (0)
Primary tumor site		
Oral cavity	13 (32.5)	10 (33.3)
Oropharynx	3 (7.5)	2 (6.7)
Hypopharynx	17 (42.5)	14 (46.6)
Larynx	3 (7.5)	2 (6.7)
Others	4 (10)	2 (6.7)
Disease status		
Local-regional failure	6 (15.4)	5 (16.7)
Distant failure	29 (74.4)	22 (73.3)
Primary distant metastasis	4 (10.3)	3 (10.0)
Previous treatment for primary tumor		
None	5 (12.5%)	3 (10.0%)
Surgery	5 (12.5%)	5 (16.7%)
Radiation	1 (2.5%)	1 (3.3%)
Chemotherapy	0 (0.0%)	0 (0.0%)
Multimodality	29 (72.5%)	21 (70.0%)
Duration between diagnosis and Gems®-cisplatin treatment (month)		
Range	0.3–122.1	0.3–122.1
Median	11.0	10.8

ITT Intent-to-treat population, *EP* evaluable population

Table 2 Best response and disease control rate in ITT and EP

Response variables	ITT		EP	
	N	%	N	%
Best response				
Complete response	0	0	0	0
Partial response[a]	9	22.5	9	30.0
Stable disease	8	20.0	7	23.3
Progressive disease	15	37.5	14	46.7
Not accessible	8	20.0	0	0
Best overall response rate	9	22.5	9	30.0
95% CI	10.8–38.5		14.7–49.4	
Disease control rate	17	42.5	16	53.3
95% CI	27.0–59.1		34.3–71.7	

ITT Intent-to-treat population, *EP* evaluable population, CI confidence interval

[a] Confirmed response (i.e., the response persisted for at least 4 weeks)

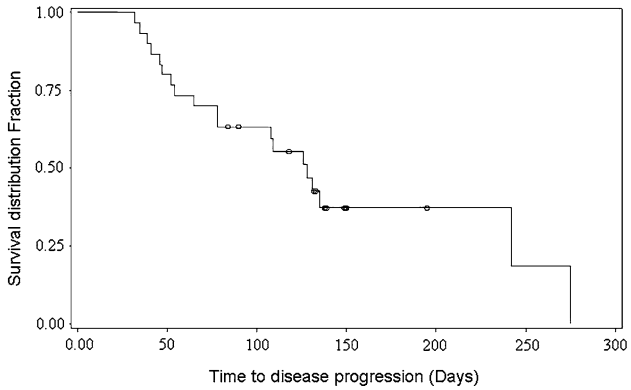

Fig. 2 Kaplan–Meier curve for time to disease progression (TTP) in evaluable patients (30 subjects). Median TTP, 128 days

in 1 case and general malaise in 1 case) or willingness of patients (3 cases); 1 case was excluded due to the tumor assessment was not confirmed by another scan 4 weeks later; 3 patients were found to violate the inclusion or exclusion criteria after enrollment; and an error of prescription was found during first course of treatment in 1 case. In these cases, no one suffered from early morbidity or mortality due to the enrollment in this trial. After dropping out from the study, all the ten cases received standard cisplatin plus 5-FU treatment. Finally, the number of intent-to-treat cases (ITT) was 40, and 30 patients were evaluable (evaluable population, EP) in the study. All of the enrolled cases were male patients. The most common primary tumor sites were hypopharynx (42.5% of ITT and 46.6% of EP), and oral cavity (32.5% of ITT and 33.3% of EP). The medium duration between diagnosis and Gems®-cisplatin treatment was 10.8 months in evaluable cases. Other details are shown in Table 1.

Treatment response and survival analysis

As shown in Table 2, the ORR was 30% (95% CI: 14.7–49.4%) in EP and 22.5% (95% CI: 10.8–38.5%) in ITT. All nine responders were PR and no complete responder was observed in our study. The disease control rare (DCR) was 53.3% (95% CI: 34.3–71.7%) in EP and 42.5% (95% CI: 27.0–59.1%) in ITT.

The response duration, time to progression and survival period were estimated in EP group. The median duration of response was 149 (95% CI: 78–161) days, the median TTP was 128 (95% CI: 78–242) days (Fig. 2), and the median OS was 401 (95% CI: 216 ~not reached) days (Fig. 3).

Safety and tolerability

The toxicity was evaluated in all 40 enrolled patients receiving Gems®-cisplatin treatment. The most prevalent

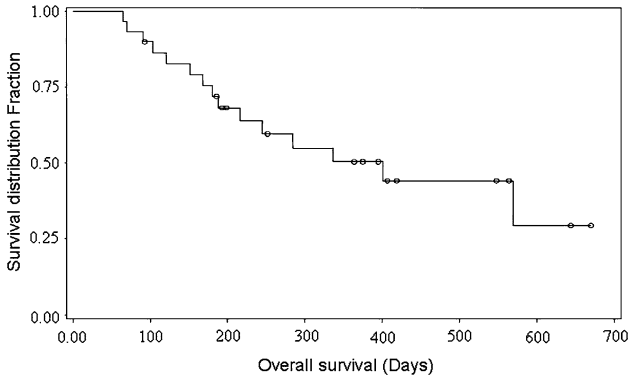

Fig. 3 Kaplan-Meier curve for overall survival (OS) in evaluable patients (30 subjects). Median OS, 307 days

toxicity is the hematologic toxicity: ≥grade 3 leukopenia was seen in 65% cases (26/40 patients), grade 3 anemia was noted in 27.5% cases (11/40 patients), and grade 3 thrombocytopenia in 10% cases (4/40 patients). No grade 4 anemia or thrombocytopenia occurred. Other grade 3 or above toxicities included infection (17.5%), nausea (5%), vomiting (2.5%), elevation of ALT (2.5%), and nephrotoxicity (2.5%). No treatment related mortality was noted in this study. The toxicity profile was detailed in Table 3.

Table 3 Frequency of chemotherapy-related adverse events graded by Common Terminology Criteria for Adverse Events (CTCAE) version 2.0 (all intent-to-treatment population)

AE category	Grade	No. of cases	%
Fever	All grades	14	35.0
	≥3	0	0
Infection	All grades	10	25.0
	≥3	7	17.5
Constipation	All grades	17	42.5
	≥3	0	0
Nausea	All grades	13	32.5
	≥3	2	5
Vomiting	All grades	15	37.5
	≥3	1	2.5
Stomatitis	All grades	1	2.5
	≥3	0	0
Anemia	All grades	31	77.5
	≥3	11	27.5
Leukopenia	All grades	32	80.0
	≥3	26	65.0
Thrombocytopenia	All grades	18	45.0
	≥3	4	10.0
Elevation of ALT	All grades	8	20.0
	≥3	1	2.5
Nephrotoxicity	All grades	4	10.0
	≥3	1	2.5
Neurotoxicity	All grades	2	5
	≥3	0	0

AE adverse effects, *ALT* alanine aminotransferase

Prognostic factor analysis

Univariate survival analysis of all evaluable cases demonstrated that prognosis was worse in cases with previous chemotherapy ($p = 0.001$), previous radiotherapy ($p = 0.027$), and without disease control before the administration of Gems®-cisplatin (i.e., no remission internal between diagnosis and initiation of GC therapy) ($p = 0.043$) (Table 4). The ORR was better in the subgroup treated with prior primary tumor excision ($p = 0.049$), but worse in the subgroup treated with prior chemotherapy ($p = 0.046$). There was no significant between-subgroup difference in DCR (Table 5).

Table 4 Univariate survival analysis in 30 evaluable cases according to clinical variables

Variables	Median OS (m)	95% CI	*P*-value[a]
Age			0.623
≤50	13.4	(6.3, 19.0)	
>50	9.5	(6.0, –)	
Duration between diagnosis and Gems®-cisplatin treatment			0.981
≤12 months	13.4	(5.6, –)	
>12 months	9.5	(6.0, –)	
Disease status			0.339
Local-regional failure	13.4	(6.0, –)	
Distant failure	9.5	(5.6, –)	
Primary distant metastasis	–	(–, –)	
Previous surgery for primary tumor			0.298
Yes	8.2	(5.6, –)	
No	13.4	(11.2, –)	
Previous chemotherapy			0.001
Yes	6.0	(4.0, 13.4)	
No	–	(9.5, –)	
Previous radiotherapy			0.027
Yes	9.5	(5.6, 19.0)	
No	–	(–, –)	
Treatment responder			0.159
Yes	19.0	(9.5, –)	
No	11.2	(5.0, –)	
Disease control before Gems®-cisplatin			0.043
Yes	19.0	(9.5, –)	
No	8.2	(3.4, –)	

OS Overall survival, *CI* Confidence interval

[a] Estimated by log-rank test

Table 5 Correlation between the overall response rate (ORR)/ disease control rate (DCR) and clinical variables in 30 evaluable patients

Variables	No.	ORR (%)	P^a	DCR (%)	P^a
Age			1.000		0.715
≤50	4/15	26.7		60.0	
>50	5/15	33.3		46.7	
Duration between diagnosis and Gems-cis treatment			0.236		1.000
≤12 months	3/16	18.8		56.3	
>12 months	6/14	42.9		50.0	
Disease status			1.000		1.000
Local-regional failure	1/5	20.0		60.0	
Distant failure	7/22	31.8		50.0	
Primary distant metastasis	1/3	33.3		66.7	
Previous surgery for primary tumor-			0.049		0.722
Yes	8/18	44.4		50.0	
No	1/12	8.3		58.3	
Previous chemotherapy			0.046		0.0813
Yes	2/16	12.5		37.5	
No	7/14	50.0		71.4	
Previous radiotherapy			0.195		0.689
Yes	5/22	22.7		50.0	
No	4/8	50.0		62.5	

[a] Estimated by Fisher's exact test

Discussion

The present study evaluated the efficacy and safety of cisplatin 80 mg/m^2 on day 8 combined with gemcitabine 1,250 mg/m^2 on days 1 and 8 recycled every 21 days in R/M SCCHN and demonstrated a good response (30% ORR in EP). The efficacy of gemcitabine in treating R/M SCCHN has been reported: in the early 1990s, a phase II study explored the efficacy and tolerability of gemcitabine monotherapy starting at 800 mg/m^2 on day 1, 8, and 15 on a 4-weekly basis in SCCHN patients pre-treated with chemotherapy, and with a higher dose (1,250 mg/m^2) in chemotherapy-naïve patients. An ORR of 13% was observed [13]. Another phase II study focused on combinations with cisplatin in 22 treatment-naïve R/M SCCHN patients, and an ORR of 22.7% was seen [17]. The response rate was better in our study than in previous ones, indicating randomized phase III studies should be carried out to confirm the result.

The prognosis of R/M SCCHN is poor: the response rates of single-agent chemotherapy (e.g., 5-fluorouracil, cisplatin or methotrexate) were 10–17% [5, 6]; even the "gold standard regimen", i.e., the cisplatin-containing combination chemotherapy, can only achieve a maximal ORR of ~30% and OS of around 6–9 months [5–7, 11]. Although taxane-containing regimen demonstrates a better ORR than cisplatin-fluouracil (CF) regimen; however, there was no significant difference of survival period between the cisplatin/paclitaxel (CP) and CF reigmen (median OS 8.7 vs. 8.1 months) [11]. Other regimen, such as a combination of cisplatin, methotrexate, bleomycin, and vincristine (CABO regimen), also did not show any survival benefit compared with CF [7]. Until recently, a pivotal study demonstrated that incorporation of an anti-EGFR monoclonal antibody (cetuximab) to the standard CF regimen can prolong both the progression-free survival (3.3 vs. 5.6 months, $p \leq 0.001$) and overall survival (7.4 vs. 10.1 months, $p = 0.04$) of R/M SCCHN cases [21]. In the present study, a promising survival period was observed: the median TTP was 128 (95% CI: 78–242) days, and the median OS was 401 (95% CI: 216 ~not reached) days. Although not in a parallel comparison, the longer median OS shown in our present study (~13.4 months) suggests confirmatory randomized phase III study is justified.

In the present trial, the most common adverse effects were ≥grade 3 hematologic toxicities, although these were not associated with increased frequency of fever and infection, and no treatment related mortality was observed. There was no ≥grade 3 neurotoxicity, and other ≥grade 3 toxicities (nausea, vomiting, and nephrotoxicity) were all seen in ≤5% of patients. Regarding the toxicities of application of gemcitabine in treating SCCHN, a phase II trial of docetaxel and gemcitabine in R/M SCCHN showed 45% case with grade 3–4 neutropenia with three treatment-related deaths [4]. Another randomized phase III trial (which compared paclitaxel/gemcitabine every 3 weeks with paclitaxel/pegylated liposomal doxorubicin every 4 weeks) showed that around 20% of patients in both study groups developed significant hematologic toxicities [14].

Other gemcitabine-containing regimens produced ≥grade 3 hematologic toxicities in 10–30% of patients [13, 17]. These results suggest that the hematologic toxicities are the major adverse effects in the gemcitabine-containing combination therapy for SCCHN. How to decrease the toxicities without reducing therapeutic benefit remains the most important issue of application of gemcitabine in the treatment of R/M SCCHN.

In conclusion, the GC regimen is associated with a good treatment response for R/M SCCHN, and no fatal toxicity was observed. It may provide an alternative for treating R/M SCCHN in addition to cisplatin/5-FU or taxane-containing regimen. A phase III randomized study is deserved to confirm the efficacy, safety and survival benefit of GC regimen in R/M SCCHN. Combination of gemcitabine with other new agents is also warranted.

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