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A Study Using Ifosfamide and Etoposide in Patients with Cisplatin-refractory Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

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Objective: To investigate the efficacy and safety of combination therapy with ifosfamide and etoposide in cisplatin-refractory recurrent/metastatic squamous cell carcinoma of the head and neck.

Methods: Thirty patients with cisplatin-refractory recurrent/metastatic squamous cell carcinoma of the head and neck were treated with ifosfamide (1000 mg/m^2/day) as a continuous 24 h infusion for 3 days and etoposide (100 mg/m^2/day) as a bolus 1 h infusion on the same 3 days. The treatment was repeated every 4 weeks until disease progression.

Results: The overall rate of response was 27% (8/30), and 20% (6/30) of the patients achieved stable disease status. Median overall survival was 7.7 months. Subgroup analysis demonstrated significant improvement in overall survival in the group that achieved control of disease. Thirteen (43.3%) patients developed grade 3–4 neutropenia, and five (16.6%) developed grade 3–4 non-hematologic mucositis.

Conclusions: This combination chemotherapy had an effective and safe profile and improved survival in patients with cisplatin-refractory recurrent/metastatic squamous cell carcinoma of the head and neck who achieved disease control.

Key words: squamous cell carcinoma – head and neck cancer – ifosfamide – etoposide – metastatic – recurrent – cisplatin-refractory

INTRODUCTION

Head and neck cancer comprises malignancies arising from the oral cavity, oropharynx, larynx and hypopharynx. It is the sixth leading cause of cancer-related deaths worldwide. The vast majority of head and neck cancers are squamous cell carcinomas. Multi-modal treatment is the mainstay for advanced stages of squamous cell carcinoma of the head and neck (SCCHN). Despite improved treatments and better locoregional control, many patients still suffer a relapse of the disease, and the prognosis of patients with R/M SCCHN is generally poor. The median overall survival (OS) is ~6–9 months (1,2). Cisplatin-based chemotherapy is the first-line treatment for R/M SCCHN. The combination of cisplatin and 5-fluorouracil (5-FU) demonstrated a superior response rate, but at the price of much greater toxicity when compared with single agents (2–4). Unfortunately, no combination therapy has been shown to improve OS.

Recently, addition of the epidermal growth factor (EGFR) antagonist cetuximab to platinum-based chemotherapy has increased OS of patients with head and neck cancer by 20% and progression-free survival by 46% compared with the standard chemotherapy group (5). This was the first phase-III trial in more than a decade that showed a survival benefit for patients with R/M SCCHN. The drawback of cetuximab is the economic burden for patients, especially considering the lack of predictive markers for the response to cetuximab treatment

(other than formation of acne after 2–3 weeks of treatment). There is still no standard treatment for patients whose disease is resistant to cisplatin, and survival is generally short for those patients. Although there have been several trials to evaluate the survival benefit of cetuximab for patients with cisplatin-refractory SCCHN, the role of cetuximab is uncertain in this group of patients. In two phase-II trials, cetuximab monotherapy or combination with cisplatin has shown activity in patients with platinum-refractory R/M SCCHN (6,7). Further phase III studies are needed.

For these reasons, there is still a need to evaluate new therapeutic regimens for treating patients with cisplatin-refractory R/M SCCHN. The rationale for combining ifosfamide with etoposide is to overcome platinum-induced resistance. Platinum-based chemotherapy kills tumor cells by binding DNA strands. The enhancement of DNA repair pathways may contribute to tolerance to platinum-induced DNA damage. The combination of ifosfamide and etoposide (IE) provides an alkylating agent (ifosfamide), which damages the DNA of the cancer cells, and etoposide, which inhibits topoisomerase II, thus blocking the repair of DNA damage induced by the alkylating agent. Ifosfamide had been studied in R/M SCCHN with overall response rate of 26% (8). In addition, etoposide, either as monotherapy (9) or in combination with cisplatin plus mitomycin (10), also demonstrated clinical benefit in R/M SCCHN. The combined two-drug regimen has shown clinical benefit in cisplatin-resistant ovarian cancer (11,12) and in various types of cancers, including soft tissue sarcomas (13). Although the combination regimen of IE achieves encouraging efficacy in platinum-resistant ovarian cancer, significant toxicity occurs (11,12). We determined the dose of IE study according to previous reports (11–13). In previous trials, ifosfamide was given at a dose of 1–1.8 gm/m^2/day for 5 days and the dosage of etoposide was 100 mg/m^2 for 3–10 days at intervals ranging from 3 to 4 weeks (11–13).Considering that our patients were heavily treated, we used a reduced dose of ifosfamide (1 g/m^2) and etoposide (100 mg/m^2) for three consecutive days in our treatment protocol compared with that in previous published studies. The reason for dose reduction was to avoid severe chemotherapy-related toxicities and the need of hematopoietic factor prophylaxis. The aim of this study was to find a regimen offering a manageable toxicity with a survival benefit in cisplatin-refractory R/M SCCHN. Therefore, the main objective of this study is to evaluate the efficacy and toxicity of this two-drug combination in heavily pretreated head and neck cancer patients.

PATIENTS AND METHODS

Patients

Patient eligibility

From September 2005 to January 2010, we prospectively evaluated patients with R/M SCCHN whose conditions were diagnosed in Taipei Veterans General Hospital, Taiwan, and who failed first-line cisplatin-based chemotherapy. Informed consents before treatment were obtained. The study was reviewed and approved by our institutional review board. The eligibility criterion was the presence of metastatic or locoregional recurrent SCCHN (unresectable and unsuitable for re-irradiation). The inclusion criteria were radiologically assessable disease; Eastern Cooperative Oncology Group performance status (ECOG PS) $\leq$2; age 18 years or greater; ECOG PS of 2 or less; leukocyte count of at least 3×10^9 cells^{-1} ; absolute neutrophil count of at least 1.5×10^9 cells^{-1}, platelet count of at least 100×10^9 cells^{-1}; prothrombin time: International Normalized ratio less than 1.5; total serum bilirubin level within normal limits; aspartate aminotransferase and alanine aminotransferase level of 2.5 times the upper limit of normal or less; and serum creatinine concentrations within normal limits. The exclusion criteria were brain metastasis proven by computed tomography (CT), significant comorbidities with major organ dysfunction and other malignancy except basal cell skin carcinoma or cervical carcinoma *in situ*.

Treatment schedule

Patients enrolled in this study were to receive 1000 mg/m^2 of ifosfamide given with mesna 1000 mg/m^2/day for 3 days and 100 mg/m^2 of etoposide per day over the same 3 days (IE therapy). Chemotherapy was given on Days 1–3 of a 28 day schedule and continued until progression of disease, unacceptable toxicity or patient withdrawal occurred. All toxicities were graded according to the National Cancer Institute's Common Toxicity Criteria (version 3.0). Decisions regarding the use of granulocyte-stimulating factors were made on an individual patient basis at the discretion of the treating physician.

Treatment and outcome evaluation

Patients were evaluated by CT of the chest and abdomen and CT or magnetic resonance imaging of the neck at baseline. Before initiation of chemotherapy, patients were also evaluated with complete history and physical examination, recording of PS, complete blood cell count and serum biochemistries. Bone scans were performed at baseline and then as clinically indicated. Evaluation of tumor response was performed every 3 months by CT. Tumor response was defined according to the Response Evaluation Criteria in Solid Tumors criteria.

Statistical methods

The Kaplan–Meier estimate was used for survival analysis, and the log-rank test was used for comparison of OS rates between groups. The response of each clinical factor was compared using the χ^2 test (for expected values $>$5) or Fisher's exact test (for expected values $\leq$5) for categorical variables. The level of statistical significance was set at a two-sided P value $<$0.05 for all tests. All statistical

analyses were made with SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient Characteristics

From September 2005 to January 2010, thirty-five consecutive cisplatin-refractory patients of head and neck cancers were treated with IE in Taipei Veterans General Hospital. Five cases with non-squamous cell histology were excluded (three small-cell carcinoma, one neuroendocrine carcinoma and one adenocystic carcinoma). Therefore, 30 patients (27 men, 3 women) were enrolled in the study. The median age of the patients was 51 years (range, 39–76 years). The patient characteristics are listed in Table 1. At initial diagnosis, the distribution of TNM (Tumor, Node, Metastasis) stages in our thirty cases is: II: 1, III: 2, IVa: 13, IVb: 6 and IVc (M1): 8.

The most common site of the primary tumor was the oropharynx (40%). The histology of 20 patients (66.7%) was moderately differentiated. The rest were well differentiated ($n = 5$, 16.7%) and poor differentiated ($n = 5$, 16.7%), respectively. The disease status of these cases when entering the IE trial is: distant metastasis (IVc): 14 locoregional recurrence: 16 (IVa: 11. IVb: 5). The median duration of disease from original diagnosis to study entry was 18.1 months. Fourteen cases had received surgery before this study (11 cases were undergone primary resection and three patients received salvage surgery for recurrent disease). All patients had previously received cisplatin alone or in combination with other agents; the most common combinations were cisplatin/FU ($n = 27$, 90%). Fourteen (46.6%) patients had received cisplatin/docetaxel. The median cycle of chemotherapy before IE therapy was four.

Table 1. Patient characteristics ($n = 30$)

	No (%)
Age (years): median (range)	51 (39–76)
Sex	
Men	27 (90.0)
Women	3 (10.0)
Performance status	
ECOG: 0/1/2	9/16/5
Smoking	23 (76.7)
BQ chewing	15 (50.0)
Alcohol drinking	17 (56.7)
Primary site	
Oral cavity	7 (23.3)
Oropharynx	12 (40.0)
Hypopharynx	6 (20.0)
Larynx	1 (3.3)
Other[a]	4 (13.3)
Site of disease recurrence	
Locoregional recurrence only	16 (53.3)
Distant metastasis	14 (46.7)
Previous initial therapy	
Surgery	11 (36.7)
Radiotherapy	22 (73.3)
Chemotherapy[b]	28 (93.3)
Previous therapy for recurrence or metastasis	
Systemic chemotherapy	27 (90.0)
Surgery	3 (10.0)
Radiotherapy	8 (26.7)
Previous platinum treatment	
Cisplatin + 5-FU	27 (90.0)
Cisplatin + taxane	14 (46.7)
Other cisplatin-based regimen	6 (20.0)
Previous chemotherapy cycle	
Median	4
Range	2–12

ECOG, Eastern Cooperative Oncology Group; BQ, betel quid; 5-FU, 5-fluorouracil.
[a]Other: two esophagus, one nasopharynx, one occult primary.
[b]Including 6 systemic chemotherapy and 22 chemotherapy incorporated with radiotherapy.

Treatment Analysis

All 30 patients received chemotherapy with IE, with a median of three cycles and a range of 1– 6. There were no complete responses (CRs) to treatment. Eight (27%) patients had a partial response (PR), whereas six (20%) achieved stable disease (SD). Sixteen patients (53.3%) demonstrated disease progression. The overall rates of response and control of disease (defined as CR + PR + SD) were 27 and 47%, respectively. The only factor significantly associated with poor control of disease was cigarette smoking (Table 2).

Toxicity

Chemotherapy-related toxicities were graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0 and are listed in Table 3. The major Grade 3 or 4 hematological toxicities were leucopenia (56.7%), neutropenia (43.3%) and anemia (16.6%). Febrile neutropenia occurred in five patients (20%). The most frequently observed severe non-hematologic toxicities were mucositis (16.6%) and nausea/vomiting (30%).

Univariate Analysis and Multivariate Analysis of OS

The OS curve estimated by Kaplan–Meier analysis for the 30 patients is shown in Fig. 1. The median survival for all

Table 2. Baseline characteristics by status of disease control

	Without disease control $n = 16$(%)	Disease control group $n = 14$(%)	P
Age >60 year	3 (18.8)	2 (14.3)	1.000
Men	15 (93.8)	12 (85.7)	0.586
ECOG PS = 1–2	13 (81.3)	7 (50.0)	0.122
Locoregional recurrence only	8 (50.0)	8 (57.1)	0.980
Primary site oropharynx	4 (25.0)	8 (57.1)	0.135
Poorly differentiated histology	3 (18.8)	2 (14.3)	1.000
Previous surgery	9 (56.3)	5 (35.7)	0.448
Smoking	15 (93.8)	8(57.1)	0.031
BQ chewing	10(62.5)	5 (35.7)	0.272
Alcohol drinking	11 (68.8)	7 (50.0)	0.501

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 3. Toxicities ($n = 30$ patients)

	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Neutropenia	2 (6.7)	9 (30.0)	5 (16.6)	8 (26.7)
Leukopenia	5 (16.6)	6 (20.0)	8 (26.7)	9 (30.0)
Anemia	9 (30.0)	12 (40.0)	4 (13.3)	1 (3.3)
Thrombocytopenia	7 (23.3)	4 (13.3)	2 (6.7)	1 (3.3)
Febrile neutropenia			3 (10.0)	2 (6.7)
Mucositis	8 (26.7)	8 (26.7)	5 (16.6)	2 (6.7)
Nausea/vomiting	9 (30.0)	7 (23.3)	9 (30.0)	0
ALT/AST	1 (3.3)	4 (13.3)	0	0
Peripheral neuropathy	0	2 (6.7)	1 (3.3)	0
Hemorrhagic cystitis	0	2 (6.7)	0	0
Renal	1 (3.3)	3 (10.0)	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

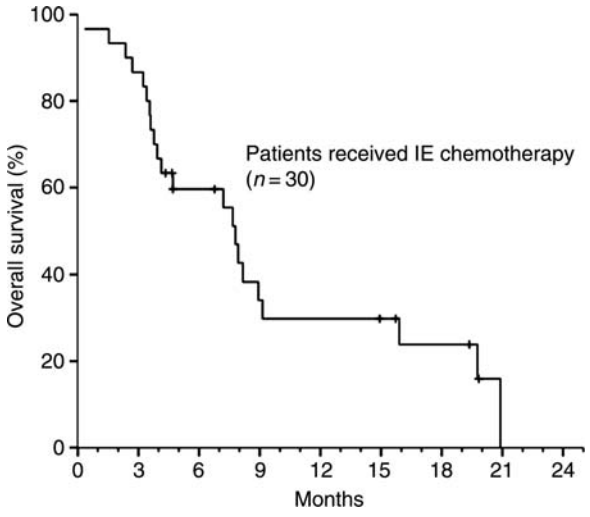

Figure 1. Kaplan–Meier estimates of overall survival (OS).

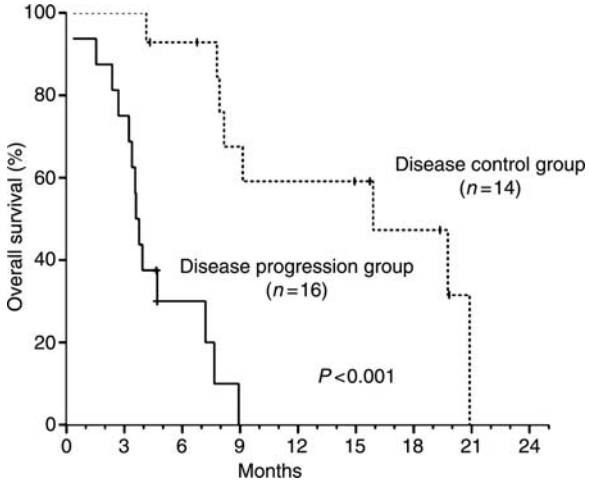

Figure 2. Kaplan–Meier estimates of OS according to the treatment response.

patients was 7.7 months. To evaluate the effect of disease controlled by IE on OS, survival analysis, using the log-rank test, was performed among patients grouped as the disease-control group ($n = 14$) and disease-progression group ($n = 16$). Significantly improved survival was demonstrated in the disease-control group (Fig. 2). The median survival periods of the disease-control and disease-progression groups were 10.7 months and 3.6 months ($P < 0.001$), respectively.

Univariate analysis for survival was conducted using the following variables: age; sex; ECOG PS; site of the primary tumor; the presence of distant metastasis; exposure to alcohol drinking, betel quid (BQ) chewing or smoking; tumor-cell differentiation and response to chemotherapy (Table 4). Exposure to cigarette smoking or BQ chewing was associated with poor survival. In contrast, patients with fair PS (ECOG = 0) or who showed a response to IE chemotherapy had a significantly better outcome. Variables with P value < 0.1 in univariate analysis were entered into the multivariate models. In multivariate analyses, disease control status under IE chemotherapy remained significantly associated with longer OS. BQ chewing and poor PS (ECOG 1–2) were associated with poor prognosis.

DISCUSSION

This study demonstrated that chemotherapy with IE had modest activity against cisplatin-refractory R/M SCCHN. Our data showed rates of response and control of disease of 27 and 47%, respectively. The combination therapy appeared to be useful for cisplatin-refractory R/M SCCHN patients, especially those who could not receive the newer generation of targeted therapies discussed below. In this study, treatment-related toxicities were modest and manageable. The major toxicities were myelosuppression, including leucopenia

Table 4. Prognostic factors for overall survival (OS), according to univariate and multivariate analyses

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age						
>60 year	1.77	0.64–4.88	0.272	–	–	–
≤60 year	1					
Men	1.99	0.45–8.73	0.361	–	–	–
Women	1					
ECOG						
PS = 1–2	3.46	1.24–9.64	0.018	4.35	1.27–14.86	0.019
0	1			1		
Metastatic	0.60	0.24–1.51	0.280	–	–	–
Locoregional only	1					
Site						
Nasopharynx	1.39	0.56–3.47	0.481	–	–	–
Oropharynx	1					
Poorly to undifferentiated histology*	0.996	0.33–3.00	0.994	–	–	–
Well to moderately differentiated histology*	1					
Previous surgery	1.26	0.53–2.99	0.594	–	–	–
Smoking	3.33	1.07–10.39	0.039	1.26	0.22–7.16	0.796
BQ chewing	2.65	1.09–6.45	0.032	3.83	1.25–11.74	0.019
Alcohol	2.26	0.91–5.64	0.080	–	–	–
Response to chemotherapy						
Disease control	0.10	0.03–0.32	<0.001	0.06	0.01–0.25	<0.001
Not disease control	1					

HR, hazard ratio; CI, confidence interval.
*According to American Joint Committee on Cancer (AJCC) Cancer Staging Manual Sixth Edition (2002).

(56.7%), neutropenia (43.3%) and anemia (16.7%). The incidence of febrile neutropenia was modest (16.7%). Grade 3 or 4 thrombocytopenia occurred in only 10% of patients. Other non-hematologic toxicities were also tolerable.

Patients with R/M SCCHN generally have a poor prognosis. Cisplatin-based chemotherapy is the most widely accepted chemotherapy regimen, with a response rate of 20–68% in the published literature (14–16). The outcome of cisplatin-refractory disease is dismal, with 2–3 months of median survival in previous retrospective reports (17). Some patients with R/M SCCHN still have good PS at the time of cisplatin failure and are candidates for second-line chemotherapy. However, there is no standard second-line therapy for cisplatin-refractory R/M SCCHN currently. New-generation chemotherapy such as taxane- and vinorelbine-based regimens had been studied in patients with platinum-refractory R/M disease (18,19). These agents are associated with response rates in the region of 20% and response durations of 5 months. Recently, the EGFR antagonist cetuximab has demonstrated a survival advantage in the setting of metastatic disease (5) Vermorken *et al*. (20) analyzed three previous trials of cetuximab efficacy against disease progression during platinum therapy. Cetuximab,(either as monotherapy or in combination with other agents), led to a response rate of 10–13%, a disease control rate of 46–56% and a median OS of 5.2–6.1 months in cisplatin-refractory R/M SCCHN(6,7,21). However, cetuximab use is limited without drug reimbursement for R/M SCCHN in Taiwan.

Several factors have been identified as predictive of better survival in patients with R/M SCCHN who are most likely benefit from treatment. They included adequate PS, a long-time interval between primary disease and recurrence, response to palliative chemotherapy and poorly differentiated histology (3,4). Unfavorable factors include weight loss and previous radiation therapy. Similarly, an analysis of two ECOG randomized trials showed that some R/M SCCHN patients may benefit from first-line cisplatin-based chemotherapy. They were more likely to have achieved an objective response to chemotherapy, have poor tumor-cell differentiation, be white, have an ECOG PS of 0 and have received no previous radiotherapy (1).

In our study, treatment response was correlated with the absence of a history of previous cigarette smoking. This finding is consistent with those of previous reports showing that tobacco use could influence the response of tumors to treatment. Further studies focusing on predictors of treatment response in cisplatin-refractory SCCHN are needed to identify the group of patients who would benefit most from second-line chemotherapy. In the univariate survival analysis, our study showed that ECOG PS 1–2 was associated with poor survival when compared with ECOG PS 0. In contrast, patients whose disease was controlled with IE chemotherapy also had better outcomes. History of cigarette smoking or BQ chewing led to a decreased OS. In the multivariate analysis of OS, disease control and good PS were still significantly associated with better prognosis after adjusting for other prognostic factors. Previous exposure to BQ chewing led to a short OS. The detrimental effect of cigarette smoking on survival was not seen in the multivariate analysis, possibly because of other confounders, including BQ chewing and response to palliative chemotherapy. BQ chewing, tobacco and alcohol have been documented as risk factors for head and neck cancer. BQ chewing is rare in the USA, Japan and Europe. On the other hand, there is an estimated 600 million people chewing betel nut worldwide, most in Southeast Asia (including Taiwan) and India. It plays an important role in carcinogenesis of squamous cell carcinoma of buccal mucosa in the above areas (22,23). Previous studies showed that BQ chewing before treatment was associated with poor survival in oral SCCHN (22,23).

Several possible mechanisms for this effect of BQ chewing were identified. The expression of p53 and $p21^{ras}$ was often higher in oral SCCHN and precancerous lesions from BQ chewers (24,25). Furthermore, safrole-like DNA adducts were frequently observed in oral squamous cell carcinoma and matched non-cancerous tissues after BQ chewing (26). Recently, overexpression of EGFR was identified in BQ-associated SCCHN. The overexpression of EGFR in SCCHN was associated with reduced recurrence-free or OS (27,28).

The limitation of our study is derived the small sample size. Although our findings are preliminary, it seems that there is a small group of these patients with cisplatin-refractory R/M SCCHN that may benefit from further treatment. Previous studies have demonstrated that single-agent chemotherapy such as docetaxel, gefitinib and cetuximab provide moderate response for R/M SCCHN patients (2). However, these drugs are not reimbursed currently for R/M SCCHN in Taiwan. We used the non-taxane containing, non-targeted therapy, which is an economic choice with acceptable toxicity and comparable efficacy in the recurrent/metastatic SCCHN. The findings of durable disease control, and the possible identification of a prognostic/predictive clinical parameter, should warrant further study of this regimen.

Therefore, we suggest that IE might be an alternative choice to taxane and target therapy in cisplatin-resistant SCCHN.

In conclusion, a regimen combining IE appeared to produce a modest activity and acceptable toxicities in patients with cisplatin-refractory R/M SCCHN. Further prospective investigation of this regimen is warranted.

Conflict of interest statement

None declared.

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