Cetuximab-based Therapy in Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma: Experience From an Area in Which Betel Nut Chewing Is Popular

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Background: This study was undertaken to evaluate the efficacy and safety of cetuximab-based therapy in recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) in an area in which betel nut chewing is popular.

Methods: Twenty-five patients were enrolled in the study from 2004 to 2008, of whom 13 received first-line cetuximab plus chemotherapy and 12 received second-line cetuximab with or without chemotherapy after the failure of cisplatin.

Results: In the first-line chemotherapy group, the overall response [complete response (CR) plus partial response (PR)] was 54% and disease control rate [CR + PR + stable disease (SD)] was 62%. In the cisplatin-failure therapy group, the overall response was 16.7% and disease control rate was 50%. Median overall survival (OS) and time to progression (TTP) in the first-line chemotherapy group were 857 days and 147 days, respectively. In the cisplatin-failure therapy group, median OS and TTP were 371 days and 136 days, respectively. The most common grade 3/4 toxicity in both groups of patients was infection/fever (23% in the first-line group, 50% in the cisplatin-failure group), followed by neutropenia (23% in the first-line group, 25% in the cisplatin-failure group).

Conclusion: Cetuximab-based therapy is an effective and safe treatment choice for recurrent/metastatic HNSCC in areas where betel nut chewing is popular. [*J Chin Med Assoc* 2010;73(6):292–299]

Key Words: betel nut, cetuximab, head and neck cancer, taxane

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the 6th most common cancer in the world. In Taiwan, it ranks 4th in male cancer-related death; in middle-age male patients between 25 and 45 years old, the occurrence of oral cancer is the highest of all cancer occurrences.[1] Most HNSCC patients in Taiwan are diagnosed at a young age, with male predominance, and with advanced disease. This unique patient population profile may be related to the habitual consumption of cigarettes, alcohol, and betel nuts.[2,3] Betel nut chewing is a common habit among those who live in South Asia, including Taiwan,[4,5] and is an etiology of HNSCC.[6] There are many compounds in the betel nut that have been correlated with carcinogenesis; the habit of chewing betel nut is related to persistent damage of the oral mucosa as well as precancerous lesions such as leukoplakia and erythroplakia, and oral fibrosis.[7] There is a high level of carcinogenic nitrosamines in the saliva of betel nut chewers, and the p53 gene mutation is correlated with the habit of betel nut chewing.[7,8] In previous reports, overexpression of epidermal growth factor receptor (EGFR) was found to be involved in betel nut-related HNSCC.[9,10]

EGFR is a tyrosine kinase receptor belonging to the ErbB family. This family includes 4 transmembrane receptors: EGFR (erbB1), HER-2 (erbB2), HER-3

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(erbB3), and HER-4 (erbB4).[11] These receptors interact with each other by heterodimerization and result in activation of intrinsic kinase activity.[12] Overexpression of EGFR has been observed in a variety of cancers such as lung, colorectal, and head and neck cancers. The anti-EGFR monoclonal antibody cetuximab (Erbitux; Merck KGaA, Darmstadt, Germany), which blocks dimerization, has been used to treat certain cancers with EGFR overexpression. In HNSCC, cetuximab combined with radiotherapy has been proven to have clinical benefit in primary treatment for organ preservation.[13] Phase II/III trials have also been conducted to evaluate the efficacy and safety of cetuximab-containing chemotherapy for recurrent/metastatic HNSCC, and the results have shown better response and prolonged survival compared with standard cisplatin-containing regimens.[14–16] Since EGFR overexpression is observed in HNSCC patients, especially in those who chew betel nut, the clinical benefit of cetuximab-based therapy in betel-nut chewing areas warrants a separate analysis.

For these reasons, we report here our experience of cetuximab-based therapy in recurrent/metastatic HNSCC patients, most of whom had a betel nut chewing habit. Response, toxicity, and survival were evaluated.

Methods

Patient population

We retrospectively analyzed 25 patients with recurrent/metastatic HNSCC who received cetuximab alone or combined with chemotherapy in Taipei Veterans General Hospital, Taiwan. Each patient signed an informed consent form for cetuximab use before treatment. Data used in our analyses were delinked from the patients' personal profiles. Exclusion criteria were age ≤18 years old, Karnofsky performance status ≤60%, inadequate hematologic, renal and hepatic function before treatment, concomitant malignancy, uncontrolled infection and any other systemic diseases.

Definition of cisplatin failure

Cisplatin failure was defined as disease progression within 6 months after the last course of cisplatin administration.

Treatment plans

All patients received cetuximab as an intravenous infusion at an initial dose of 400 mg/m^2 followed by 250 mg/m^2 every week. Concomitant chemotherapy included cisplatin 100 mg/m^2 every 3 weeks or docetaxel 80 mg/m^2 every 3 weeks; or combination therapy [cisplatin 75 mg/m^2 or carboplatin (area under the curve = 4) on day 1 and 5-fluorouracil 1,000 mg/m^2 on days 1–4 every 3 weeks; cisplatin 75 mg/m^2 on day 1 and docetaxel 75 mg/m^2 or paclitaxel 150 mg/m^2 on day 1 every 3 weeks]. Treatment was continued until disease progression, clinical deterioration, or the appearance of intolerable adverse effects.

Response and toxicity assessment

Treatment response was evaluated by the RECIST criteria.[17] Evaluation of response to treatment was performed every 3 months. Toxicity was graded according to the National Cancer Institute's *Common Toxicity Criteria*.[18]

Statistical analysis

All analyses were done using SPSS version 14.0 (SPSS Inc., Chicago, IL, USA). Overall survival (OS) was defined as the time from the start of cetuximab treatment to the date of death or the date last seen. Time to progression (TTP) was defined as the time from the start of cetuximab treatment to the date of disease progression or the date of the last follow-up. Median and life tables were computed using the product-limit estimate of the Kaplan-Meier method, and the log-rank test was applied for the comparison of survival periods between groups. The response analysis of each clinical factor was compared using the χ^2 or Fisher's exact test for categorical variables. Two-sided p values less than 0.05 were considered statistically significant.

Results

Patient characteristics

From 2004 to 2008, 25 patients with recurrent/metastatic HNSCC were enrolled in the study. There were 23 male and 2 female patients; 15 (60%) had a betel nut chewing habit. The median follow-up time was 370 days (range, 70–1,153 days). Thirteen patients received first-line cetuximab plus chemotherapy (77% were taxane-containing and 75% were cisplatin-containing regimens; data not shown), and the other 12 patients received second-line cetuximab-based therapy (25% were cetuximab monotherapy and 75% were cetuximab combined with chemotherapy) after cisplatin failure for recurrent/metastatic HNSCC. The demographic characteristics of the 2 groups were similar, with the exception of distant metastasis (67% *vs.* 23%, $p = 0.003$) and taxane-containing chemotherapy (77% *vs.* 17%, $p = 0.01$) (Table 1).

Treatment response

In the 13 patients who received first-line cetuximab-based therapy as treatment for recurrent/metastatic HNSCC, 3 (23%) achieved complete response (CR), 4 (31%) achieved partial response (PR) and 1 (8%) had stable disease (SD). The overall response rate to cetuximab-based therapy as first-line treatment was 54%, and the disease control rate was 62%. Among these 13 patients, 10 received taxane-containing regimens while 3 received non-taxane-containing regimens. A trend of increased complete response (30% *vs.* 0%) was observed in the group who received taxane-containing regimens. The response profile of using cetuximab-containing regimen as first-line therapy for recurrent/metastatic HNSCC is shown in Table 2.

Twelve patients received cetuximab as second-line therapy after the failure of cisplatin treatment. One (8.3%) patient with CR, 1 (8.3%) with PR, and 4 (33.3%) with SD were observed. The overall response and disease control rates were 16.7% and 50%, respectively. Among these 12 patients, 3 (25%) received cetuximab monotherapy; only 1 (33.3%) PR was observed, with no CR or SD. The other 9 patients who received cetuximab combined with chemotherapy showed 1 CR (11.1%) and 4 SD (44.4%). The disease control rate was better in the cetuximab plus chemotherapy group

Table 1. Characteristics of the 25 patients who received cetuximab-based therapy for recurrent/metastatic head and neck squamous cell carcinoma*

	First-line cetuximab + chemotherapy ($n = 13$)	Cisplatin-failure chemotherapy ($n = 12$)	p
Age	54 (36–81)	58 (43–76)	0.42
Sex			0.95
Male	12 (92.3)	11 (92)	
Female	1 (7.7)	1 (8)	
Betel nut chewing			0.69
Yes	7 (54)	8 (67)	
No	6 (46)	4 (33)	
Primary site			0.80
Oral cavity	3 (23)	2 (17)	
Oropharynx	1 (8)	1 (8)	
Hypopharynx	3 (23)	5 (42)	
Larynx	2 (15)	1 (8)	
Unknown primary	4 (31)	3 (25)	
Recurrent/metastatic sites			0.003
Local recurrence	8 (62)	1 (8)	
Lung metastasis	2 (15)	3 (25)	
Multiple metastases	3 (23)	8 (67)	
Combined chemotherapy			0.01
Taxane-containing	10 (77)	2 (17)	
Non-taxane-containing	3 (23)	7 (58)	
Without combination	0 (0)	3 (25)	
Cetuximab cycles	6 (1–12)	5 (1–11)	0.59

**Data presented as median (range) or n (%).*

Table 2. Responses of the 13 patients to first-line cetuximab plus chemotherapy for recurrent/metastatic head and neck squamous cell carcinoma*

	Taxane-containing ($n = 10$)	Non-taxane-containing ($n = 3$)	p	Overall ($n = 13$)
CR	3 (30)	0 (0)	0.28	3 (23)
PR	2 (20)	2 (66.7)	0.13	4 (31)
SD	1 (10)	0 (0)	0.57	1 (8)
PD	4 (40)	1 (33.3)	0.84	5 (38)

**Data presented as n (%). CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.*

than in the cetuximab monotherapy group (55.6% *vs.* 33.3%). The results of using cetuximab-based therapy as second-line treatment after cisplatin failure are shown in Table 3.

To identify the predictors of treatment response, several clinical factors were analyzed in all 25 patients. Only cisplatin status showed a significant difference in overall response (54% *vs.* 16.7%, $p=0.05$) (Table 4).

Survival analysis

In the 13 patients who received first-line chemotherapy for recurrent/metastatic HNSCC, median OS and TTP were 857 days and 147 days, respectively (Figures 1 and 2). In the 12 patients who received chemotherapy for cisplatin-failure recurrent/metastatic HNSCC, median OS was 371 days and median TTP was 136 days (Figures 1 and 2). Betel nut chewing status and survival were evaluated: the OS of patients who chewed and those who did not chew betel nut were 371 days and 493 days ($p=0.34$), respectively, and the TTPs were 135 days and 154 days ($p=0.54$), respectively (Figures 3 and 4).

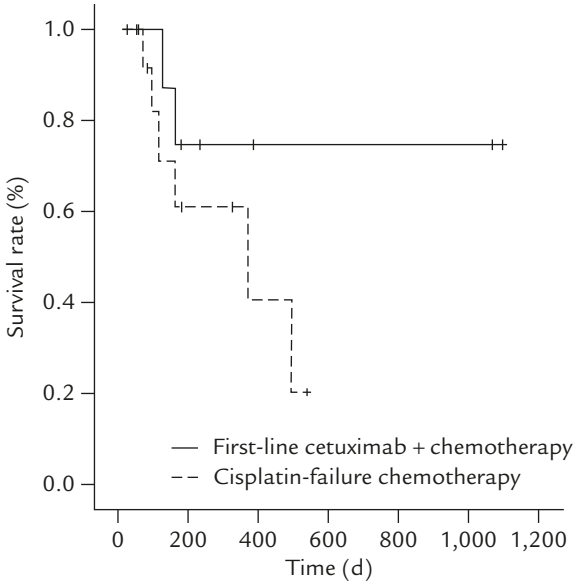

Figure 1. Kaplan-Meier overall survival curves for patients with recurrent/metastatic head and neck squamous cell carcinoma who received first-line or cisplatin-failure cetuximab chemotherapy (median, 857 days *vs.* 371 days; $p=0.167$).

Table 3. Responses of the 12 patients to cisplatin-failure chemotherapy for recurrent/metastatic head and neck squamous cell carcinoma*

	Cetuximab monotherapy ($n=3$)	Cetuximab combination chemotherapy ($n=9$)	*p*	Overall ($n=12$)
CR	0 (0)	1 (11.1)	0.55	1 (8.3)
PR	1 (33.3)	0 (0)	0.07	1 (8.3)
SD	0 (0)	4 (44.4)	0.16	4 (33.3)
PD	2 (66.7)	4 (44.4)	0.51	6 (50.0)

**Data presented as n (%). CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.*

Table 4. Responses of patients with different clinical characteristics to treatment for recurrent/metastatic head and neck squamous cell carcinoma*

	CR + PR	*p*	CR + PR + SD	*p*
Betel nut chewing habit		0.73		0.74
Yes	5 (33)		8 (53)	
No	4 (40)		6 (60)	
Platinum status		0.05		0.56
Cisplatin failure	2 (20)		6 (50)	
No cisplatin failure	7 (54)		8 (62)	
Taxane		0.16		0.82
Yes	6 (50)		7 (54)	
No	3 (23)		3 (23)	
Cetuximab		0.62		0.17
With chemotherapy	8 (38)		13 (62)	
Without chemotherapy	1 (25)		1 (25)	

**Data presented as n (%). CR = complete response; PR = partial response; SD = stable disease.*

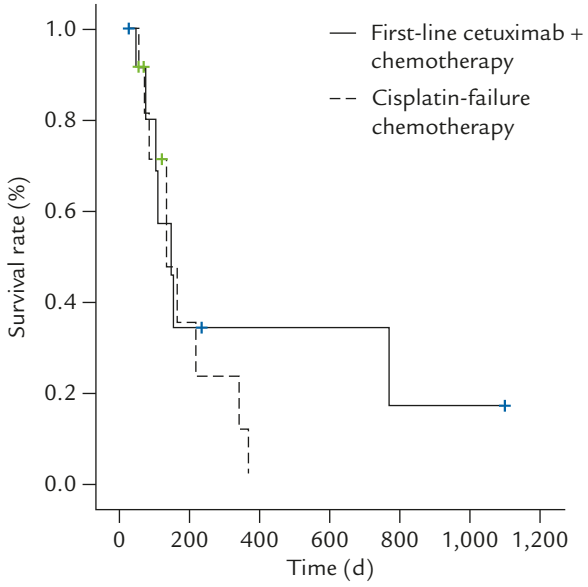

Figure 2. Kaplan-Meier time-to-progression curves for patients with recurrent/metastatic head and neck squamous cell carcinoma who received first-line or cisplatin-failure cetuximab chemotherapy (median, 147 days *vs.* 136 days; $p = 0.48$).

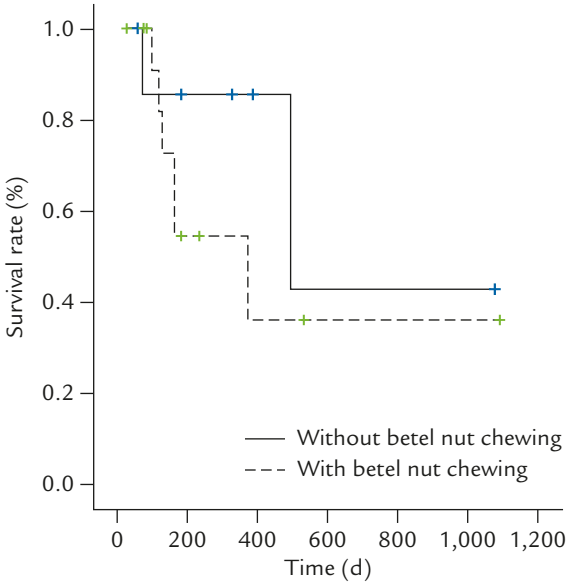

Figure 3. Kaplan-Meier overall survival curves for patients with recurrent/metastatic head and neck squamous cell carcinoma who have or do not have a betel nut chewing habit (median, 371 days *vs.* 493 days; $p = 0.34$).

Toxicity

We analyzed the toxicities of cetuximab and chemotherapy together. As shown in Table 5, the most common grade 3/4 toxicities with first-line cetuximab-based therapy were infection/fever (23%) and neutropenia (23%). Other grade 3/4 toxicities included mucositis/stomatitis (8%), dysphagia (8%), and acne-like rash (8%). With second-line cetuximab-based therapy, the most common toxicity was infection/fever (50%), followed by neutropenia (25%), anemia (16.7%), thrombocytopenia (8.3%), dysphagia (8.3%), weight loss (8.3%), and acne-like rash (8.3%).

Discussion

In this study, we demonstrated that cetuximab-based chemotherapy increased the response and survival in patients with recurrent/metastatic HNSCC in an area where betel nut chewing is popular. The prognosis of recurrent/metastatic HNSCC has been poor. Even with cisplatin-containing chemotherapy, the objective maximal response rate that could be achieved was about 30%, and OS was around 6–9 months.[19–23] In a recent phase III trial, adding cetuximab to first-line cisplatin-based chemotherapy for the treatment of recurrent/metastatic HNSCC significantly improved the response to about 40% and OS to 10 months.[16] As the first representative results from an area where betel nut chewing is popular, our findings are consistent with those of the previous large-scale study.[16] It is interesting to note that betel nut chewing does not seem to be related to poor response and survival (Figures 3 and 4). A possible explanation is that most patients with a betel nut chewing habit have a higher EGFR gene copy

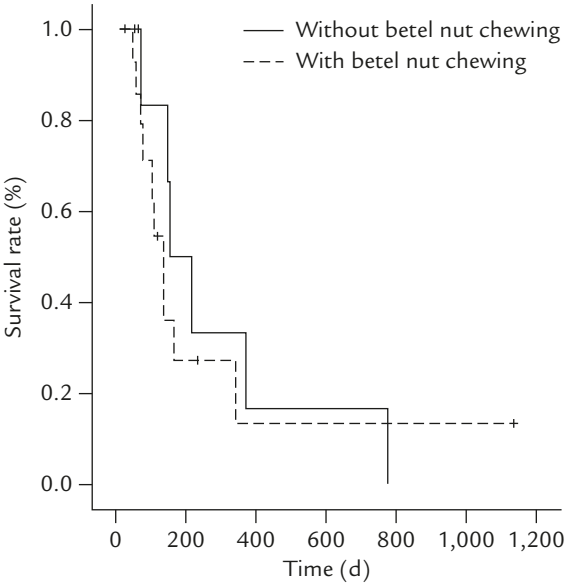

Figure 4. Kaplan-Meier time-to-progression curves for patients with recurrent/metastatic head and neck squamous cell carcinoma who have or do not have a betel nut chewing habit (median, 135 days *vs.* 154 days; $p = 0.54$).

Table 5. Common toxicities in the 25 patients who received cetuximab-based therapy for recurrent/metastatic head and neck squamous cell carcinoma*

	First-line cetuximab + chemotherapy ($n = 13$)	Cisplatin-failure chemotherapy ($n = 12$)
NCICTC grade	3–4	3–4
Mucositis/stomatitis	1 (8)	0 (0)
Dysphagia	1 (8)	1 (8.3)
Nausea	0 (0)	0 (0)
Vomiting	0 (0)	0 (0)
Diarrhea/constipation	0 (0)	0 (0)
Infection/fever	3 (23)	6 (50.0)
Weight loss	0 (0)	1 (8.3)
Neutropenia	3 (23)	3 (25.0)
Anemia	0 (0)	2 (16.7)
Thrombocytopenia	0 (0)	1 (8.3)
Acne-like rash	1 (8)	1 (8.3)

**Data presented as n (%) except for NCICTC grade. NCICTC = National Cancer Institute Common Toxicity Criteria.*

number,[9] which is thought to be a determining factor of the response to cetuximab treatment.[24] This explanation, however, needs further studies for verification.

A significant proportion of patients (48%) in this study accepted taxane-containing chemotherapy. The major consideration to add taxane to chemotherapy regimens is that taxane is an effective chemotherapy in HNSCC and in combination with platinum; it shows better therapeutic effects than conventional cisplatin/5-fluorouracil regimens.[25–27] Although the results of the current study are preliminary and the case number was relatively small, taxane-containing chemotherapy seemed to lead to a better response than non-taxane chemotherapy (overall response rate, 50% *vs.* 23%; disease control rate, 54% *vs.* 23%), especially for the first-line cases (CR, 30% *vs.* 0%; Table 2). The combination of cetuximab and taxane is well-tolerated. There are ongoing trials to determine the effect of combining these 2 agents in the treatment of HNSCC.[28,29] However, large-scale pivotal studies are warranted to confirm the efficacy and safety.

The prognosis in patients after cisplatin failure is particularly poor, and response rates are generally < 5%.[30] Some phase II trials have explored the possible role of cetuximab alone or in combination with a platinum compound.[14,15] The results suggest that combined cetuximab and platinum-based chemotherapy is an active and well-tolerated treatment choice. In previous reports, cetuximab did not increase the toxicity of combined chemotherapy, and there did not appear to be any difference in response between single-agent and combination cetuximab therapy.[14,15,31] Vermorken et al summarized 3 previous prospective studies of second-line cetuximab treatment of recurrent/metastatic HNSCC after cisplatin failure and reported an overall response rate of 10–13%, and a disease control rate of 46–56%.[32] Haddad and Shin summarized 3 other prospective studies of first-line combination cetuximab therapy for recurrent/metastatic HNSCC and reported an overall response rate of 26.3–35.6%, and OS of 9.2–10.4 months.[33] In the current study, cetuximab combined with chemotherapy seemed to result in better response than cetuximab monotherapy (disease control rate, 56% *vs.* 33%). A possible explanation is that 2 (17%) patients accepted taxane-containing chemotherapy, and 1 (8%) achieved CR while 1 (8%) had SD. There was an interesting observation that TTP was almost the same in the first-line chemotherapy and cisplatin-failure therapy groups (147/136 days). A possible explanation is that in the 1st treatment arm of the study population, there were 2 patient subgroups, which were those with controlled disease versus those with uncontrolled disease. The patients with controlled disease had much better survival than the patients with uncontrolled disease (due to the still high response to second-line cisplatin-failure chemotherapy), and such a phenomenon could explain why similar TTPs were observed. However, it was difficult to further analyze the data due to the very small patient numbers.

With regard to toxicity profile, there were no additive toxicities when we compared the 22 patients who received combination therapies with the 3 patients who received cetuximab monotherapy. This finding is compatible with that of previous studies. Since the incidence of grade 3/4 toxicity did not increase significantly (infection/fever, 50% in combination therapy *vs.* 66.7% in monotherapy, data not shown), using taxanes rather than platinum combined with cetuximab in platinum-failure HNSCC could be considered in patients with good performance status.

In conclusion, our report is the first to demonstrate the efficacy and safety of using cetuximab-based therapy in recurrent/metastatic HNSCC from an area where betel nut chewing is popular. We also showed the efficacy and safety of combining cetuximab with taxanes in recurrent/metastatic HNSCC, both in first-line and platinum failure settings. Further large-scale trials are warranted to confirm these observations.

Acknowledgments

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