A Phase II Single Institution Study of Docetaxel in Patients with Recurrent and/or Metastatic Non-Nasopharyngeal Squamous Cell Carcinoma of the Head and Neck Refractory to a Platinum-Based Chemotherapy

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Abstract: Background/Aim: The taxanes has been proved to be active for treatment of many cancers. We conducted a phase II study to investigate the efficacy and tolerability of weekly docetaxel in patients with platinum-refractory recurrent and / or metastatic squamous cell carcinoma of the head and neck (SCCHN). Patients & Methods: Patients with metastatic or recurrent SCCHN and adequate hematologic, renal and hepatic function and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 were enrolled. Prior platinum-based chemotherapy with or without radiotherapy were permitted with 4-week interval. The regimen was weekly docetaxel (30 mg/m2) administered for 4 weeks every 5 weeks for a maximum of 6 cycles. Patients with disease progression or unacceptable toxicity were excluded from the study. Results: Fifty-five patients with a median age of 53 years (range, 39 –73 years) were accrued. Previously, most patients had received radiotherapy and chemotherapy, and a majority of patients had treatment-free interval of < 6 months. All patients who were entered on the study were assessable for toxicity and response of docetaxel. There was 9 clinical responses (16.4%, {95% confidence interval, 8. 9 - 28.3}) and another 16 (29.1% {95% confidence interval, 18.8-42.2}) had stable disease. Disease control rate was 45.5% (95% confidence interval, 33.1-58.5). No Grade 3–4 toxicities were recorded. The most common hematological toxicity was grade 1-2 anemia in 46 patients (83.7%), and non-hematological toxicities were mild and manageable. The estimated median progression-free and median overall survival times were 4 (95% confidence interval, 3.1-4.9; SE: 0.46) and 8 months, (95% confidence interval, 5.9- 10.1; SE: 1.1) respectively, and the 1-year overall survival rate was 12.7%.There was no treatment-related death. Conclusion: The results of this study suggested that, in the population with platinum-refractory, recurrent and/or metastatic squamous cell carcinoma of the head and neck, weekly docetaxel regimen had good clinical activity with an acceptable toxicity.

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Key words: head and neck carcinoma, squamous cell carcinoma, platinum refractory, recurrent/ metastatic tumor, weekly docetaxel, chemotherapy.

1. Introduction:

Squamous cell carcinoma of the head and neck (SCCHN) is a major public health problem that frequently causes devastating consequences to the functions, economics and cosmetic appearance of its victims, as well as death. It is the sixth most common malignancy, with 500,000 patients worldwide[1].The 2009 estimated number of head and neck cancer in the US is of 35,720 new cases[2].

Sixty percent of primary SCCHN recurs after aggressive standard therapy and 5–25% develops distant metastases[3,4]. For these patients, platinum-based chemotherapy is commonly used and has demonstrated survival advantages over the best supportive care[5,6]. However, treatment options for recurrent squamous cell carcinoma of the head and neck (SCCHN) following platinum-based therapy are limited[7,8].

Recurrent and metastatic squamous cell carcinoma of the head and neck still carries a poor prognosis. Response rates with combination chemotherapy regimens are generally higher than those observed with single-agent chemotherapy. However, this did not translate into an overall survival benefit [9,10]. Thus as none of the combination chemotherapy regimens demonstrated an overall survival benefit when compared with single-agent

chemotherapy, the use of combination chemotherapy outside clinical trials is usually restricted to younger patients with a good performance status and with symptomatic disease who require prompt symptom relief[9,10].

Recurrent, unresectable head and neck squamous cancer is a complex problem. Evidence for the efficacy of treatment is scant in this area and given the large number of patient and tumor variables involved in the recurrent tumor, several factors play a role in deciding the choice of management. The results of treatment are very poor and associated with significant toxicity. Thus, the quality of life outcome following treatment should play a major role in the choice of treatment[11].

The taxanes play a significant role in the treatment of various solid tumors of epithelial origin[12]. Docetaxel (a semisynthetic taxane) is one of the most effective chemotherapeutic agents against cancer[13], and is the most extensively studied taxane in prospective head and neck cancer trials and has been investigated as induction chemotherapy or in combination with radiotherapy in locally advanced squamous cell carcinomas of the head and neck and as palliation in recurrent or metastatic disease[12,14-19]. Hematologic toxicity was the major problem in those studies, because most patients with recurrent or metastatic SCCHN have debilitating conditions and enhanced toxicity.

The aim of this study was to investigate the efficacy and tolerability of weekly docetaxel regimen in patients with platinum-refractory recurrent and/or metastatic squamous cell carcinoma of the head and neck.

2. Patients and Methods:

Patient Characteristics & inclusion criteria:

Patient eligibility criteria included histologically confirmed SCCHN (except the nasopharynx) that recurred after previous platinum-based chemotherapy (Platinum-refractory disease was defined as cancer with documented tumor progression (PD) during platinum-based treatment or recurrence within 6 months after platinum-based chemoradiotherapy), with or without radiotherapy and/or surgery, or which presented with distant metastases at the time of initial diagnosis; measurable disease; Eastern Cooperative Oncology Group (ECOG) performance status[20] of 0–2, age 18–75 years; adequate bone marrow (WBC ≥ 4000/ml, absolute neutrophil count ≥1500/ml and platelet ≥100 000/ml), normal liver and renal function tests, no brain parenchymal or leptomeningeal metastases; and no other previous or concurrent malignancy. Patient was excluded if previous chemotherapy regimen containing taxanes.

Previous radiotherapy or chemotherapy for adjuvant therapy or relapsed disease is allowed if treatment was completed at least 4 weeks before the enrollment into this study.

All patients signed an informed consent before the initiation of any treatment.

Treatment Protocol:

This was single-arm and phase II clinical trial. The regimen consisted of docetaxel 30 mg/m2 delivered as an intravenous infusion over 60 min. Treatment was administered weekly for 4 weeks, every 5 weeks. Treatment was maintained for a maximum of six courses. Patients with disease progression or unacceptable toxicity were excluded from the study.

Patients were premedicated with dexamethasone, diphenhydramine and cimetidine to reduce the risk of anaphylaxis. Antiemetics were administered at the discretion of the treating physician.

Before every cycle, a complete recovery of the patient's blood count was required. Dose modifications or delays in administration were applied on the basis of nadir counts and toxicities of the last cycle. Delays that lasted ≥ 2 weeks were not allowed, and those patients were removed from the study.

Response Evaluation:

Tumor response assessments were performed after every two cycles of treatment. Criteria of complete response, partial response, stable disease and progressive disease were based on the standard definitions of the WHO. Evaluation was done using computed tomography (CT) to diagnose any progression of target lesion and to identify any emerging new lesions.

Toxicity Evaluation:

Toxicity grading was based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 3.0).

Statistical analysis:

Overall survival was calculated from the time of start of chemotherapy until death or last follow-up according to the Kaplan-Meier method[21] with SPSS [Statistical package] (version 9.0). Mean and standard deviation were estimates of quantitative data. The 95% confidence intervals (95% CIs) were calculated with the exact method. Overall survival and progression-free survival were compared by the Kaplan–Meier method[21] with statistical significance assessed by the log-rank test. All *P* values were two-tailed; a value of ≤ 0.05 was considered significant.

3. Results

Patient characteristics:

A total of 55 consecutive platinum-refractory SCCHN (except the nasopharynx) patients were treated at Clinical Oncology Department, Faculty of Medicine, Tanta University, Egypt and enrolled in this phase II trial from December 2005 to January 2009. The patient characteristics of all enrolled patients are listed in Table 1. The median age of study participants was 53 years (range, 39–73 years, standard deviation ± 6.77) , 83.6% of who were male. The primary tumor sites were: larynx, twenty two (40%); oral cavity, nine (16.36%); Paranasal sinuses, four (7.27); hypopharynx, nine (16.36%) and oropharynx, eleven (20%). All patients had previously received platinum-based chemotherapy treatment and 43.6% underwent surgery, while 94.54% of the patients were treated with radiotherapy (median dose, 66 grays [Gy]; range, 50–72 Gy).The majority of the patients had relapse or progression to previous treatment within 6 months. Sixty percent of the patients presented with an ECOG performance status of 2.

At initial diagnosis 52 patients (94.54%) had Stage III–IV disease. The majority of recurrences were locoregional (76.36). All distant metastases were located in the bone, liver and/or lung.

Table 1. Baseline Demographic and Clinical Characteristics (*N* = 55 patients)

Characteristic	No. of patients (%)
Age (years)	
Median	53
Mean	54.3
Range	39–73
Sex	
Male	46 (83.6)
Female	9(16.4)
Male to female ratio	5.1 : 1
ECOG performance status at diagnosis	
1	22(40)
2	33 (60)
Location of primary tumor	
Larynx	22 (40)
Oropharynx	11 (20)
Hippopharynx	9(16.36)
Oral cavity	9 (16.36)
Paranasal sinus	4 (7.27)
Initial stage at diagnosis	
Stage II	3(5.45)
Stage III	40 (72.72)
Stage IV	12 (21.82)
Therapy of the primary tumor	
Chemotherapy and radiotherapy	31 (56.36)
Chemotherapy, radiotherapy, and surgery	17 (38.18)
Surgery and chemotherapy	3(5.45)
Recent platinum therapy	
Cisplatin -based	42 (76.36)
Carboplatin-based	13 (23.64)
Location of recurrent disease	
local or regional relapse	42 (76.36)
Distant metastases	3(5.45)
both loco-regional relapse and Distant metastases	10 (18.18)

Treatment

Totally, 196 administrations of docetaxel were administered and evaluated. The median number of chemotherapy cycles was three (range 2–6).

All cycles were initiated at the initial planned doses, and no treatment delays because of toxicity were reported.

Response to Treatment

No complete responses were observed, while 9 patients had partial response with response rate of

16.4% (95% CI, 8. 9 - 28.3). Stable disease was observed in 16 patients (29.1%), whereas the other 30 patients (54.5%) had progressive disease, (Table 2).

Patients failed on the docetaxel regimen, (30 patients) received best supportive care and further treatment was at the physician's discretion. The response to salvage chemotherapy and/or radiation therapy was not recorded as part of our study.

Survival

All patients died during the observation period. The Median progression-free survival and overall survival times were 4 months (95% confidence interval, 3.1-4.9; SE: 0.46) and 8 months (95% confidence interval, 5.9- 10.1; SE: 1.1), respectively, and the 1-year overall survival rate was 12.7% (Fig.1, 2).

Table 2. Tumor response (*N* = 55 patients)

Response	No. of patients	%	95% confidence interval
Partial response	9	16.4	8. 9 - 28.3
Stable disease	16	29.1	18.8-42.2
Progressive disease	30	54.5	41.5-66.9
Tumor control rate (PR + SD)	25	45.5	33.1-58.5

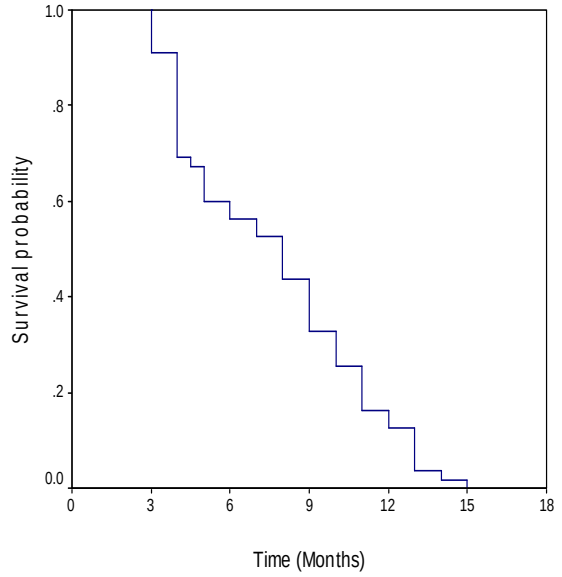

Figure 1. Kaplan–Meier curve of overall survival. Median overall survival time was 8 months.

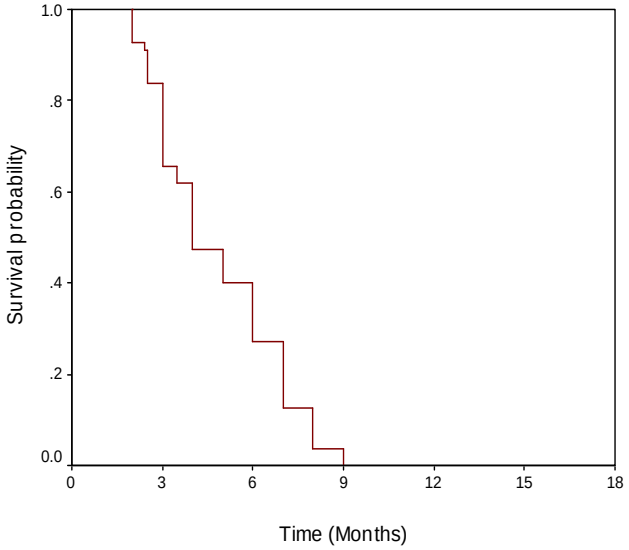

Figure 2. Kaplan–Meier curve of progression-free survival. Median progression-free survival time was 4 months.

Toxicity

The most common adverse reactions to this regimen are listed in Table 3. No Grade 3– 4 toxicities were reported. The main hematologic toxicity was Grade 1–2 anemia, which occurred in 83.7% of patients. Grade 1–2 neutropenia occurred in 40.1% of patients.

Grade 1 thrombocytopenia was recorded in 23.6% of patients. Other non-hematological toxicities were mild and manageable. No patients discontinued therapy because of toxicity. No one died due to treatment-related toxicity.

Table 3. Hematologic and Non-hematologic Toxicity (*N* = 55 patients)

	Grade 1		Grade 2	
Toxicity	**No.**	**%**	**No.**	**%**
Non-hematologic Toxicity				
Alopecia	19	34.6	25	45.5
Anorexia	13	23.6	10	18.2
Stomatitis/ pharyngitis	5	9.1	3	5.5
Nausea/vomiting	0	0	3	5.5
Paresthesia	0	0	3	5.5
Asthenia	19	34.6	29	52.7

Conjunctivitis	2	3.6	0	0
Diarrhea	3	5.5	2	3.6
Onycholysis	13	23.6	19	34.6
Hematologic Toxicity				
Neutropenia	19	34.6	3	5.5
Anemia	36	65.5	10	18.2
Leucopenia	20	36.4	5	9.1
Thrombocytopenia	13	23.6	0	0

4. Discussion:

Palliative chemotherapy has demonstrated survival advantages over best supportive care for advanced SCCHN patients[22], and the most commonly used agents are cisplatin or carboplatin, generally in combination regimens with infusional fluorouracil or a taxane. Only approximately one-third of patients will respond to first-line platinum-based therapy, and the median overall survival time can be expected to be approximately 6–9 months. However, there is no standard treatment in the relapsed or refractory patients. The rate of response to second-line chemotherapy was shown to be largely dependent on the therapy regimen given. Patients with advanced SCCHN have limited alternative therapeutic options once they progress on platinum-based chemotherapy, and response rates are generally poor (3–10%)[23,24].The overall survival time was 56 days with best supportive care and remained short as 3.3–4.6 months despite 25% of disease control rate with aggressive intervention.

In this study, the weekly administration of a single-agent docetaxel for the treatment of platinum-refractory SCCHN appeared to have good clinical efficacy (16.4% overall response rate and a median overall survival of 8 months) and an acceptable safety profile.

Other single agents that are used in the treatment of patients with recurrent head and neck carcinoma, such as methotrexate, reportedly had response rate of 23%, with a median response duration of 84 days [25]. In another trial, the response rate of 16% with methotrexate in patients with advanced head and neck carcinoma, was reported[26]. However the response rate was dropped into 10% in Forastiere et al.[27] trial with methotrexate in patients with advanced head and neck carcinoma. In our study, the overall response of 16.4% was nearly similar to that reported by Grose et al.[26].

The combination with targeted agent such as cetuximab may be considered to increase the response with acceptable toxicities in patient of refractory SCCHN[28], however, cetuximab has limited role and could not be used widely for SCCHN patients in our country because of limited resources. Herbst et al.[29] reported the results of a cetuximab and cisplatin regimen and found that median overall survival was 4.3 months and response rate was 6% in patients with documented PD or recurrence within 3 months of platinum-based therapy. Baselga et al.[28] showed a median overall survival of 5.0 months with a response rate of 11% in platinum refractory patients treated with cetuximab followed by platinum chemotherapy. In our study, the median overall survival was 8 months for a similar population. So our report appeared to be useful especially for those platinum-refractory SCCHN patients

A number of trials of docetaxel for head and neck cancer have been reported[14,19,30-37]. Dreyfuss et al.[32] reported an overall response rate for docetaxel (100 mg/m2) in incurable and metastatic SCCHN patients without prior chemotherapy of 42%, although dose reduction as a result of neutropenia was frequent. Couteau et al.[33] reported a median overall survival of 6.7 months, with the most frequent side-effect being short-term neutropenia (grade 4: 79.2%). Docetaxel (100 mg/m2) therapy was thought to be tolerable for patients in good condition, but toxic in patients who had received prior platinum-based chemotherapy.

Several studies that tested weekly docetaxel found that the dose-limiting toxicity was hematologic toxicity and recommended doses between 34 mg/m2 per week up to 43 mg/m2 per week[38-40].

Our treatment schedules and doses were selected based on other previous pilot studies[14,19,41]. We used a low dose of docetaxel (Weekly 30 mg/m2 administered for 4 weeks every 5 weeks for a maximum of 6 cycles) because of the kind of patients who were included. The majority of our patients showed malnutrition, frailty, disease recurrences, and previous treatment for primary disease. The median number of chemotherapy cycles was three (range 2–6). Patients with disease progression or unacceptable toxicity were excluded from the study.

Some previous reports have described efforts to reduce the toxicity of single therapy with docetaxel[14,19,35-37]. In particular, Hitt et al.[19] reported that single weekly docetaxel at 30 mg/m^2 did not induce grade 3–4 hematological toxicity and gave an overall response rate of 42% in 38 patients with recurrent or metastatic disease and no prior

chemotherapy. Thus weekly docetaxel administration is considered an effective means of reducing toxicity. In our study the toxicity profile of this regimen was acceptable, with no Grade 3–4 treatment-related toxicities. Grade 1–2 anemia occurred in 46 patients (83.7%), probably because of the poor initial performance status of the study population and their poor nutritional status. Asthenia, and alopecia were the most commonly reported Grade 2 toxicities. The frequency of these toxicities was somewhat higher than previously reported in other Phase II studies with weekly docetaxel[19,38,42]. However, the 40.1% Grade 1–2 neutropenia in our study is lower than the 70– 91% severe neutropenia in other studies of taxanes achieving high response without G-CSF support[23,43,44].

However, in our study, the overall response of 16.4%, the median progression-free survival of 4 months, the median overall survival of 8 months and the 1-year overall survival rate of 12.7%, were lower than that reported in Hitt et al.[19] study in which the overall response rate was 42%, the 1-year overall survival rate was 39% and the estimated median overall survival and progression-free survival were 11.3 months and 10 months respectively. There are three possible explanations. First, treatment-refractory disease presented in this trial. Secondly, five patients die before the first evaluation due to rapid disease progression. Usually, patients with life expectance, 3 months will not be included in clinical trials. But, this may be representative for our daily practice in refractory SCCHN instead of selection bias for production a good response phase II trial. Thirdly, a higher percentage of relative poor performance was presented in this study population. Sixty percent of the patients had an ECOG performance status of >1. Many studies demonstrated significantly higher risk of death in patients with low performance status, when they were receiving chemotherapy[45-47]. These three factors would confound each other and all affected by the first one. The selection bias of platinum-refractory patients may be the main reason why this trial achieved lower results than Hitt et al.[19] study.

About 76% of the patients included in our series had locoregional recurrences, and all of them had received previous platinum-based chemotherapy. The objective response rate was significantly higher in patients who had baseline ECOG performance status of <2 (p=0.05), and in those patients with primary laryngeal tumors (P = 0.01), however, the number of patients in this study was low.

In conclusion, weekly docetaxel regimen is active in patients with platinum-refractory recurrent and/or metastatic SCCHN, and shows an excellent toxicity profile.

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