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ORIGINAL ARTICLE

Weekly docetaxel in patients with platinum-refractory metastatic or recurrent squamous cell carcinoma of the head and neck

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Abstract
Background The objective of the study was to investigate the efficacy and tolerability of weekly docetaxel in patients with platinum-refractory recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN).
Methods Patients fulfilling the following criteria were enrolled: histologically confirmed SCCHN; documented progressive disease (PD) after platinum-based treatment; Eastern Cooperative Oncology Group (ECOG) 0–2; measurable disease; not candidates for local therapy. Docetaxel (35 mg/m^2) was administered for 3 weeks, every 4 weeks for a maximum of 6 cycles.
Results A total of 23 patients were treated. All patients were assessable for toxicity and response. The overall response rate was 13.0% (3/23) and disease control rate was 34.7% (8/23). Median progression-free and overall survival (OS) was 9 (95% CI, 7.6–10.4 weeks) and 29 weeks (95% CI, 10.8–47.1 weeks), respectively. Most common hematological toxicities were grade 1–2 anemia (6/23, 26.1%) and nonhematological toxicities were mild and manageable. There was no treatment-related death.
Conclusion Weekly docetaxel regimen had good clinical activity with an acceptable toxicity in patients with platinum-refractory SCCHN.

Keywords Docetaxel · Head and neck · Squamous cell carcinoma · Chemotherapy · Platinum-refractory

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Introduction

Squamous cell carcinoma of the head and neck (SCCHN) is the sixth-most common cancer in the world [1]. The majority of patients with SCCHN present with locally advanced disease that requires a combination of chemotherapy, radiotherapy, or surgery [2, 3]. Concurrent administration of cisplatin with radiation is considered as the nonsurgical standard therapeutic modality for such patients [4–6] and is also the standard adjuvant therapy for high-risk postoperative patients [7–9]. Results with this modality, however, generally have been disappointing, with a cure rate of <30%. In addition, approximately 10% of patients have distant metastases at the time of initial presentation and up to 20% as a site of relapse [10].

Recurrent or metastatic SCCHN (R/M-SCCHN) is generally incurable and is associated with poor survival [11, 12]. Platinum-based palliative chemotherapy consisting of either cisplatin or carboplatin is the usual first-line treatment for these patients, resulting in median survival of 6 months and 1-year survival rate of 20%. Unfortunately, however, patients with advanced SCCHN have limited alternative therapeutic options once they progress on platinum-based treatment, and responses are rare (approximately 3%) and usually of brief duration [13]. Thus, there is clearly an unmet therapeutic need of active agents for the treatment of this poor prognosis patient population with no standard treatment approach.

Docetaxel has proven major activity in the treatment of SCCHN and has been investigated as induction chemotherapy [14, 15] or in combination with radiotherapy in locally advanced SCCHN [16] and as palliation in recurrent or metastatic disease [17–20]. Phase II trials assessing single agent docetaxel, given at a dose of 100 mg/m^2 every 3 weeks to chemotherapy-naive patients with R/M-SCCHN, have demonstrated response rates of 21–42% [21].

The most common toxicity observed with the standard 3-weekly docetaxel regimen (100 mg/m^2) was myelosuppression and its complications, neutropenic fever and/or infection [12, 18]. Other observed toxicities have included alopecia, gastrointestinal toxicity, acute anaphylactoid-type reaction, and fluid retention. The toxicity profile of docetaxel means that the 3-weekly regimen is unlikely to be tolerated by some patients, particularly patients who have poor performance status or have reduced bone-marrow reserves owing to prior platinum-based chemotherapy.

In an attempt to alter the toxicity profile, investigators conducted several clinical trials of docetaxel administered by weekly schedules in patients with advanced cancers [22–25]. These trials demonstrated that weekly dosing with docetaxel 30–36 mg/m^2 was active and well tolerated with low incidences of grade 3 or 4 myelosuppression and hematologic toxicity. This has led to speculation that weekly dosing may improve the therapeutic index of docetaxel and may be more suitable for patients who are unable to tolerate the 3-weekly regimen. In particular, Hitt et al. [26] reported that single weekly docetaxel at 30 mg/m^2 did not induce grade 3 or 4 hematological toxicity and gave an overall response rate of 42% in 38 R/M-SCCHN patients without prior chemotherapy. However, efficacy of weekly docetaxel in R/M-SCCHN patients who have progressed on platinum-based treatment remains unknown [27].

Therefore, the aim of the present study was to investigate the efficacy and tolerability of weekly docetaxel at 35 mg/m^2 in the treatment of platinum-refractory SCCHN.

Patients and methods

Patient eligibility

Patients fulfilling the following criteria were enrolled: histologically confirmed SCCHN; documented progressive disease (PD) after platinum-based treatment; an Eastern Cooperative Oncology Group (ECOG) performance scale of 0–2; not candidates for local therapy; measurable metastatic lesions as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST); and adequate hematologic, hepatic, and renal functions. The disease was staged according to American Joint Committee on Cancer (AJCC) Staging System. All patients gave written consent before the initiation of any treatment.

Treatment

Docetaxel was administered intravenously over 60 min at 35 mg/m^2 on days 1, 8, and 15 of a 4-week cycle for a maximum of 6 cycles. Cycles were administered on an outpatient basis. All patients received premedication with a total of 3 doses of dexamethasone, each consisting of 4 mg given orally every 12 h, 50 mg diphenhydramine, and 50 mg of ranitidine given intravenously.

Evaluation of response and toxicity

For each patient, baseline evaluations included a complete physical examination, computed tomography (CT), and/or magnetic resonance imaging (MRI) of the target lesion, blood-cell count, serum chemistry and electrolytes. Before receiving each dose of docetaxel, patients underwent a complete blood-cell count. Blood chemistry studies were repeated before each treatment cycle. Radiologic assessments were performed only after two treatment cycles unless required earlier because of clinical situation.

Response criteria were based on the Response Evaluation Criteria in Solid Tumor (RECIST) Committee [28]. If a patient was documented as having a complete response (CR) or a partial response (PR), a confirmatory evaluation was performed after 4 weeks.

Toxicity was recorded according to the National Cancer Institute Common Toxicity Criteria (version 3.0). Chemotherapy was delayed by 7 days in case of absolute neutrophil count <1,000/mm^3 or platelet count <100,000/mm^3. For grades 3 or 4 nonhematologic toxicities and neutropenia with fever (1 oral temperature >38.5°C or 3 oral temperatures of >38°C in a 24-h period) or infection, treatment was withheld until the toxic effect resolved to grade 1 and was then reinstituted at a 25% dose reduction.

Survival and statistical analysis

The primary objective of the study was to assess overall response rate (ORR) and toxicity of weekly docetaxel monotherapy in platinum-refractory SCCHN. The secondary objective was to assess disease control rate (DCR), progression-free survival, and overall survival (OS). Disease control was defined as a combination of CR, PR, and stable disease (SD) as best response. OS was defined as the period from the start of treatment to the date of death. Time to progression (TTP) was defined as the period from the start of treatment to the date when disease progression or death was observed. DCRs and RRs were compared between demographic factors using Fisher's exact test. The survival

distribution was estimated by the Kaplan–Meier method. PFS and OS were compared between demographic factors using the log-rank test.

Results

Patient characteristics

A total of 23 platinum-refractory SCCHN patients were recruited. Patient characteristics are listed in Table 1. The median age was 55 years (range, 37–75 years), and the majority of patients (87%) were male. More than half of the patients (52.2%) had an ECOG performance status of 2. The majority of patients had AJCC stage III (26.1%) or IV (47.8%) squamous cell carcinoma at the time of initial diagnosis. The most common site of the primary tumor was the oral cavity (34.8%), and approximately half of the patients (56.5%) had metastatic disease. Cisplatin-based concurrent chemoradiotherapy or combination chemotherapy was the most common prior therapy, whereas 2 patients received combination chemotherapy with carboplatin, of which total cumulative dose were 500 and 975 mg/m^2, respectively, and 5-fluorouracil. The median dose of prior cisplatin exposure was 160 mg/m^2 (range, 80–500 mg/m^2). Median time from initial diagnosis to docetaxel therapy was 8 months (range, 2–21 months). The median time from the end of platinum-based chemotherapy to the first dose of docetaxel was 5 weeks (range, 2–52 weeks), and the median time to progression on the most recent platinum therapy was 16 weeks (range, 4–69 weeks). Serum albumin concentrations at baseline were lower than 4.0 g/dL in 15 patients (65.2%), which suggested the poor nutritional status of the patients in our series.

Table 1 Patient characteristics

Characteristic	No. of patients (%) (n = 23)
Median age in years (range)	55 (37–75)
Gender	
Male	20 (87.0)
Female	3 (13.0)
ECOG performance status	
1	11 (47.8)
2	12 (52.2)
Initial stage at diagnosis	
Stage II	6 (26.1)
Stage III	6 (26.1)
Stage IV	11 (47.8)
Location of primary tumor	
Oral cavity	8 (34.8)
Larynx	1 (4.3)
Oropharynx	4 (17.4)
Hypopharynx	4 (17.4)
Nasopharynx	4 (17.4)
Paranasal sinus	2 (8.7)
Location of recurrent disease	
Locoregional	10 (43.5)
Distant	2 (8.7)
Locoregional and distant	11 (47.8)
Therapy of the primary tumor	
Chemotherapy alone	3 (13.0)
Chemotherapy and radiotherapy	7 (30.4)
Chemotherapy, radiotherapy, and surgery	13 (56.5)
Disease duration, months (range)	8 (2–21)
Median TTP on platinum therapy, weeks (range)	16 (4–69)

Abbreviation: *ECOG*, Eastern Cooperative Oncology Group; *TTP*, time to progression

Compliance with treatment

Total cycles of administration of weekly docetaxel were 63 cycles (median, 2 cycles; range, 1–6 cycles). Treatment delays for a brief period were reported in 6 patients (26.1%) because of grade 2 paronychia (2 patients), grade 2 thrombocytopenia (1 patient), grade 3 neutropenia (2 patients), and grade 3 diarrhea with dehydration (1 patient), respectively. However, no patient discontinued treatment because of toxicity. The median docetaxel total dose received per patient was 210 mg (range, 70–630 mg), and the median dose intensity was 26.25 mg/m^2 per week (range, 14.0–26.25 mg/m^2 per week).

Tumor response and survival

Responses in all 23 evaluable patients included 3 PR, 5 SD, and 15 PD, producing RR of 13.0% (95% CI, 7.8–26.0%) and DCR of 34.7% (95% CI, 20.8–69.5%), respectively (Table 2). The primary site and response duration for patients who achieved a partial response was nasopharynx (24 weeks), oral cavity (19 weeks), and hypopharynx (8 weeks), respectively.

With a median follow-up duration of 20 weeks (range, 4–108 weeks), the median TTP and OS were 9 (95% CI, 7.6–10.4 weeks) and 29 weeks (95% CI, 10.8–47.2 weeks), respectively (Fig. 1). The characteristics favoring a prolonged OS were higher baseline ECOG scale (36 vs. 20 weeks in patients with ECOG of 2), disease control (32 vs. 20 weeks in patients with progressive disease), and higher baseline serum albumin concentration (36 vs. 20 weeks in patients with albumin of <4.0 g/dL), although there were no significant differences observed.

Table 2 Response to treatment

Response (RECIST criteria)	No. of patients (n = 23)	%
Complete response (CR)	0	0
Partial response (PR)	3	13.0
Stable disease (SD)	5	21.7
Progressive disease (PD)	15	65.2
Disease control rate (DCR)	34.7	
95% CI (%)	20.8–69.5	
Overall response rate, CR + PR	13.0	
95% CI (%)	7.8–26.0	

Abbreviations: *RECIST*, Response Evaluation Criteria in Solid Tumor; *DCR*, CR + PR + SD

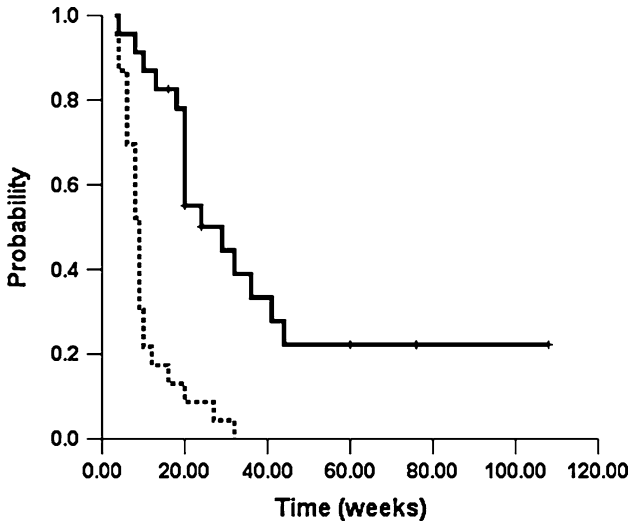

Fig. 1 Kaplan–Meier survival curves showing time to progression (TTP; *black dotted line*) and overall survival (OS; *black solid line*) rates for all patients (n = 23). The median TTP and median OS were 9 (95% CI, 7.6–10.4 weeks) and 29 weeks (95% CI, 10.8–47.2 weeks), respectively

After disease progression on docetaxel, 14 patients (60.9%) received subsequent treatments; S-1 (8 patients), gemcitabine (2 patients), and others (4 patients).

Toxicity

Toxicity assessment of the 23 patients who received treatment is described in Table 3. The most frequent hematologic toxicities were anemia (7 patients, 29.2%) and neutropenia (3 patients, 12.5%). The only grade 3 or 4 hematologic toxicity was neutropenia, which was observed in 2 patients (8.3%).

The most frequent nonhematologic toxicities were anorexia (8 patients, 34.8%), asthenia (7 patients, 30.4%), nausea (4 patients, 17.4%), and mucositis (4 patients, 17.4%). Grade 3 diarrhea with subsequent dehydration occurred in one patient (4.3%). There was no treatment-related death in the study.

Table 3 Hematologic and nonhematologic toxicity (n = 23 patients)

Toxicity	Grade 1–2		Grade 3	
	No.	%	No.	%
Hematologic				
Neutropenia	1	4.3	2	8.7
Anemia	6	26.1	0	0
Thrombocytopenia	1	4.3	0	0
Nonhematologic				
Febrile neutropenia	0	0	0	0
Conjunctivitis	2	8.7	0	0
Infection	1	4.3	0	0
Neuropathy	2	8.7	0	0
Headache	1	4.3	0	0
Constipation	1	4.3	0	0
Mucositis	4	17.4	0	0
Edema	1	4.3	0	0
Paronychia	2	8.7	0	0
Dehydration	0	0	1[a]	4.3
Diarrhea	3	13.0	1[a]	4.3
Asthenia	7	30.4	0	0
Anorexia	8	34.8	0	0
Nausea	4	17.4	0	0

[a] These grade 3 toxicities occurred in one patient

Discussion

Although several previous trials reported the activity of single agent docetaxel as a first-line treatment of R/M-SCCHN [17–20, 26], to our knowledge, this is the first study to assess efficacy of weekly administration of docetaxel (35 mg/m^2) in platinum-refractory SCCHN patients. In the current study, the weekly docetaxel regimen achieved ORR of 13.0% and a median survival of 29 weeks, which demonstrates that this regimen has good activity in this population of platinum-refractory SCCHN patients. Given that prognosis of platinum-refractory R/M-SCCHN patients, for whom there is currently no standard treatment approach, is poor and the median survival in this population with best supportive care was only 56 days [13], our results with acceptable toxicity profile are encouraging and warrant further investigation of this regimen in order to confirm benefit in terms of survival.

Second-line treatment with 3-weekly docetaxel regimen after failure of a platinum-based chemotherapy in

R/M-SCCHN has been previously reported [27, 29]. In the study by Zenda et al. [27], 20 patients with platinum-refractory disease received 60 mg/m^2 of docetaxel every 3–4 weeks. Overall response rate was 10%, with the most frequent adverse event being leucopenia (grade 4, 35%) and neutropenia (grade 4, 30%). Numico et al. [29] reported an ORR for docetaxel administered at 80 mg/m^2 every 3 weeks of 11%, although hematologic and/or nonhematologic toxicities were more frequent than those reported in our study.

Generally, 3-weekly docetaxel regimen has been reported to be active, but myelosuppression may make this schedule unsuitable for heavily-pretreated and poor performance status patients [23]. The toxicity profile of weekly regimen in our study was excellent, with grade 3 hematologic toxicity observed in 2 patients (8.7%), confirming that weekly administration of docetaxel was considered an effective means of reducing toxicity. Reducing toxicity was particularly important in the patient population, who had poor prognostic features, enrolled in the present study. More than half of the patients had undergone every treatment modalities available (chemotherapy, radiotherapy, and surgery) before docetaxel treatment, had poor performance status (ECOG performance status of 2 in 52.2% of patients), and presented with hypoalbuminemia at baseline, which has been associated with poor outcomes in SCCHN [30].

Recently, cetuximab alone or in combination with cisplatin produced major objective responses with acceptable toxicity in patients with platinum-refractory R/M-SCCHN [31–33]. In a phase II study of single agent cetuxiamb reported by Vermorken et al. [33], ORR was 13%, DCR was 46%, median TTP was 70 days, and OS was 178 days, respectively. These results are quite similar to those from our study.

In conclusion, the current study shows that weekly docetaxel regimen has good clinical activity with an acceptable toxicity in patients with platinum-refractory R/M-SCCHN.

Conflict of interest statement The authors indicated no potential conflicts of interest.

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