Original Articles

Single-agent Docetaxel in Patients with Platinum-refractory Metastatic or Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN)

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Background: The objective of this retrospective study was to investigate the efficacy and tolerability of single-agent docetaxel in patients with platinum-refractory squamous cell carcinoma of the head and neck (SCCHN).

Methods: Platinum-refractory disease was defined as cancer with documented tumor progression during platinum-based treatment or recurrence within 6 months after platinum-based chemoradiotherapy. Patients fulfilling the following criteria were enrolled: histologically confirmed SCCHN, excluding nasopharyngeal cancer; measurable metastatic lesions as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST); and platinum-refractory disease. Docetaxel (60 mg/m2) was administered every 3–4 weeks and continued unless there was evidence of disease progression or unacceptable toxicity.

Results: Twenty patients were recruited. Overall response rate was 10% (2/20) and tumor control rate was 25% (5/20). Median progression-free and median overall survival times were 1.7 and 4.6 months, respectively. The most common hematological toxicities were leucopenia (grade 4: 35%) and neutropenia (grade 4: 30%). Grade 3 febrile neutropenia and grade 3 mucositis (functional/symptomatic) each occurred in two patients (10%). One fatal bleeding occurred during this treatment, however, the relation between this event and docetaxel was unlikely. Median inpatient period during treatment was 5.4 days (range, 0–50 days).

Conclusion: A single-agent docetaxel regimen appeared to offer an acceptable clinical profile in patients with platinum-refractory SCCHN.

Key words: docetaxel — squamous cell carcinoma — head and neck — chemotherapy — platinum refractory

INTRODUCTION

Squamous cell carcinoma of the head and neck (SCCHN) is the sixth-most common cancer in the world (1). The majority of patients present with locally or regionally advanced disease (2,3). Single-agent cisplatin with concurrent radiotherapy is the nonsurgical standard of care for locally advanced SCCHN patients (4–6), and is also considered the standard adjuvant therapy for high-risk post-operative patients (7–9). However, approximately 10% of patients with SCCHN have distant metastasis at the time of initial presentation. For these patients, platinum-based chemotherapy is commonly used and has demonstrated survival advantages over the best supportive care (10,11).

Unfortunately, however, alternative therapeutic options for patients with advanced SCCHN are limited once platinum-based treatment has failed. Leon et al. (12) investigated best supportive care for patients with platinum-refractory SCCHN and showed a median survival time of 56 days. Herbst et al. (13) reported that median overall survival was 4.3 months and response rate was 6% in platinum-refractory...
patients treated with cetuximab and cisplatin regimen. Then, the prognosis of platinum-refractory SCCHN patients remains poor.

Docetaxel has shown extensive antitumor activity against various common cancers in clinical studies. In Japan, Inuyama et al. reported the efficacy of single-agent docetaxel 60 mg/m² tri-weekly or monthly for previously treated or metastatic SCCHN, with an overall response rate of 22.2% (14). In this retrospective study, we investigated the efficacy and tolerability of tri-weekly or monthly single-agent docetaxel at 60 mg/m² in the treatment of platinum-refractory SCCHN.

PATIENTS AND METHODS

PATIENTS

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. Patients fulfilling the following criteria were enrolled: histologically confirmed SCCHN, excluding nasopharyngeal cancer; measurable metastatic lesions as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) (15); and platinum-refractory disease. Written informed consent to treatment was obtained from all patients before the initiation of any treatment.

TREATMENT SCHEDULE

Docetaxel was given by single intravenous infusion at 60 mg/m² over 1–2 h. Treatment was repeated every 3–4 weeks and continued unless there was evidence of disease progression or unacceptable toxicity. Routine premedication against hypersensitivity reaction was not performed. The protocol provided for a decrease in docetaxel dose in patients experiencing grade 4 hematological toxicity or grade 3 non-hematological toxicities.

RESPONSE EVALUATION

Response to treatment was assessed using the RECIST criteria. Evaluation was done using computed tomography (CT) owing to its convenient diagnosis of target lesion progress and identification of emerging new lesions. Basically, CT evaluations were performed every 6–8 weeks.

TOXICITY

Toxicities were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTCAE ver. 3.0). Treatment period was defined as the period from the initiation of therapy to 3 weeks after the last day of administration of docetaxel. To evaluate tolerance in outpatients, assessment was also done during hospitalization in those patients requiring hospitalization during the course of the study.

STATISTIC ANALYSIS

Overall survival was measured from the first day of study treatment until death. Survival functions were computed using the Kaplan–Meier method (16).

RESULTS

PATIENT CHARACTERISTICS

Thirty-five consecutive platinum-refractory SCCHN patients were treated at Shizuoka Cancer Center between September 2002 and April 2006. Of these, 15 patients were treated by other regimens, leaving 20 patients were recruited into the study. Patient characteristics are listed in Table 1.

According to the UICC criteria (17), 18 patients (90%) had clinical stage IV disease before first-line treatment. Cisplatin (CDDP) and 5-fluorouracil (5-FU) with concurrent radiotherapy was the most common prior treatment.

EXPOSURE TO DOCETAXEL THERAPY

A total of 50 administrations of docetaxel were given. The median number of docetaxel cycles was two (range 1–7), and dose intensity was 15.6 mg/m²/week. Treatment was continued until tumor progression in 19 patients (95%). Fatal bleeding from the primary site during the treatment period occurred in one (5%), for which treatment was discontinued.

Table 1. Patient characteristics

<table>
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<th>No. of patients</th>
<th>Median (range)</th>
<th>Male/Female</th>
<th>0/1/2</th>
<th>8/10/2</th>
<th>One regimen</th>
<th>Two regimens</th>
<th>Three regimens</th>
<th>CDDP-based</th>
<th>Carboplatin</th>
<th>Nedaplatin</th>
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<td>8/10/2</td>
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CDDP, Cisplatin.
After the docetaxel regimen failed, eight patients received best supportive care including palliative radiotherapy. The details of the next treatment for other patients were as follows: S-1 regimen, 4; nedaplatin (CDGP) regimen, 4; others, 4.

RESPONSE AND SURVIVAL

All patients died during the observation period. Overall response rate was 10% (2/20), and tumor control rate (partial response and stable disease) was 25% (5/20) according to the RECIST criteria (Table 2). Median progression-free survival and overall survival were 1.9 and 4.6 months, respectively (Fig. 1).

TOXICITY

The major adverse reactions to docetaxel are listed in Table 3. The most common hematological toxicities were leucopenia (grade 4: 35%) and neutropenia (grade 4: 30%). Grade 3 febrile neutropenia and grade 3 mucositis (functional/symptomatic) each occurred in two patients (10%). One fatal bleeding occurred during this treatment, however, any relation between this event and docetaxel was unlikely.

Overall treatment period was 1456 days. Overall inpatient period was 205 days (14%) and median inpatient period was 4.5 days (range 0–50 days). Eight (40%) of 20 patients remained outpatients throughout the treatment period. A total of 13 hospitalizations occurred, as follows: deterioration in performance status (PS) in three patients, febrile neutropenia in three, infection in two, hematological toxicity in one, severe mucositis in one and other reasons unrelated to toxicity in three.

DISCUSSION

In this study, a single-agent docetaxel (60 mg/m²) regimen for the treatment of platinum-refractory SCCHN appeared to have good clinical efficacy and an acceptable safety profile. The prognosis of platinum-refractory SCCHN patients was poor and the median survival in this population with best supportive care was only 56 days (12).

There have been several trials to improve survival of patients with platinum-refractory SCCHN. Herbst et al. (13) 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. (18) 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, overall response was 10% and median overall survival was 4.6 months for a similar population.

Because cetuximab could not be used for SCCHN patients in Japan, our report appeared to be useful especially for Japanese platinum-refractory SCCHN patients. A number of trials of docetaxel for head and neck cancer have been reported (14,19–26). Dreyfuss et al. (20) 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. (21) 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. Then, docetaxel was administered every 3 or 4 weeks at a dose of 60 mg/m² in the present study, as reported in a previous Japanese phase II study (14,22). Hematological toxicity was moderate (grade 4 neutropenia: 30%) and febrile neutropenia occurred in two patients (10%), but no treatment-related deaths were seen.

Because our regimen was basically conducted on an outpatient basis, we considered that inpatient period may represent an objective index of feasibility. Overall inpatient period was 205 days, accounting for 14% of the total treatment period. Median inpatient period per one patient was 4.5 days (range 0–50 days), and eight patients (40%) remained outpatients throughout the treatment period. These findings suggest the feasibility of this treatment for outpatient cancer chemotherapy. Therefore, this dose and schedule were considered appropriate for this population.

However, some previous reports have described efforts to reduce the toxicity of single therapy with docetaxel (23–26). In particular, Hitt et al. (25) reported that single weekly docetaxel at 30 mg/m² 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. Weekly administration is considered an effective means of reducing toxicity, although efficacy in patients with platinum-refractory disease remains controversial.

In conclusion, a single-agent docetaxel (60 mg/m²) regimen appeared to offer an acceptable clinical profile in patients with platinum-refractory SCCHN. Further prospective investigation of this regimen to optimize doses and scheduling is necessary.

Acknowledgment

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Conflict of interest statement

None declared.

References

