The Feasibility Study of Docetaxel in Patients with Anaplastic Thyroid Cancer

Kenji Kawada1,2,*, Koichi Kitagawa1, Sachi Kamei1, Megumi Inada1, Ayako Mitsuma1, Masataka Sawaki1, Toyone Kikumori3, Yasushi Fujimoto4, Hiroshi Arima5, Tsuneo Imai3 and Yuichi Ando1

1Department of Clinical Oncology and Chemotherapy, Nagoya University Hospital, 2Department of Medical Oncology, Japanese Red Cross Nagoya First Hospital, 3Department of Breast and Endocrine Surgery, Nagoya University Hospital, 4Department of Otorhinolaryngology, Nagoya University Hospital and 5Department of Endocrinology and Diabetes, Nagoya University Hospital, Nagoya, Aichi, Japan

*For reprints and all correspondence: Kenji Kawada, Department of Medical Oncology, Japanese Red Cross Nagoya First Hospital, 3-35 Michishita-cho, Nakamura-ku, Nagoya, Aichi 453-8511, Japan. E-mail: kekawada@nagoya-1st.jrc.or.jp

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There is no established chemotherapy for anaplastic thyroid cancer. We conducted a prospective feasibility study at a single center to explore the antitumor activity of docetaxel against anaplastic thyroid cancer. Docetaxel was administered intravenously at a dose of 60 mg/m² over the course of 1 h every 3 weeks in patients with anaplastic thyroid cancer who had received no prior chemotherapy. A total of seven patients with anaplastic thyroid cancer were enrolled over the course of 30 months and received docetaxel. The treatment response was complete response in one patient, stable disease in two and progressive disease in four. The response rate was 14%, and the disease control rate (complete response plus stable disease) was 43%. The median time to progression was 6 weeks (range, 1–50). Toxicity was tolerable. Docetaxel could be an effective drug for the treatment of anaplastic thyroid cancer, with tolerable toxicity.

Key words: anaplastic thyroid cancer – docetaxel – chemotherapy

INTRODUCTION

Anaplastic thyroid cancer (ATC) is one of the most aggressive human malignant tumors (1). The median survival of patients with ATC generally ranges from 3 to 6 months from the time of diagnosis with a 1-year survival rate of about 10%, much poorer than outcomes in patients with other well-differentiated thyroid cancers. Although ATC accounts for less than 2% of all primary thyroid malignancies, it thus is responsible for 14–39% of all deaths from thyroid cancer (1,2). Unfortunately, standard care for this lethal disease has not been established because of its aggressive behavior, rarity and resistance to chemotherapy. Surgery and radiation therapy for primary lesions in the neck can palliate symptoms and may prolong survival (3–5). However, potential benefits of systemic chemotherapy, targeting distant metastases as well as local lesions, remain to be fully explored.

Doxorubicin has been a key drug for the treatment of ATC, producing response rates ranging from 5% to 22%, and is considered more effective in combination with cisplatin (6–12). In a recent Phase II study, 10 of 19 assessable patients with ATC responded to paclitaxel for a response rate of 53%, including 1 complete response and 9 partial responses (12). Both doxorubicin and paclitaxel might be clinically effective against ATC, but standard chemotherapy for ATC remains controversial. Docetaxel is another taxane that is currently used clinically. Similar to paclitaxel, docetaxel acts by promoting and stabilizing microtubule assembly and has been shown to be as clinically effective as paclitaxel against many solid cancers. To our knowledge, however, the efficacy of docetaxel against ATC has not been evaluated clinically. We conducted this prospective feasibility study of docetaxel with antitumor activity as the primary endpoint in patients with ATC.
PATIENTS AND METHODS

PATIENTS

Patients older than 20 years were eligible for this study if they had pathologically confirmed ATC, no prior chemotherapy, at least one measurable lesion that could be assessed according to the response evaluation criteria in solid tumors (RECIST), an Eastern Cooperative Oncology Group performance status of 0–2, adequate hematologic function (neutrophil count ≥1500/mm³, platelets ≥100 000/mm³ and hemoglobin ≥9.0 g/dl), adequate liver function (total bilirubin ≤1.5 mg/dl, aspartate aminotransferase ≤100 IU/l and alanine aminotransferase ≤100 IU/l) and adequate renal function (serum creatinine ≤1.5 mg/dl).

This study was approved by the Institutional Review Boards of Nagoya University Hospital. All patients gave written informed consent.

STUDY DESIGN

This was an open-label, single-center, prospective feasibility study of docetaxel in patients with ATC; the primary endpoint was the response rate (UMIN000000482). Docetaxel was administered intravenously at a dose of 60 mg/m² over the course of 1 h every 3 weeks until disease progression. Patients received 8 mg of dexamethasone intravenously plus a 5-hydroxytryptamine receptor antagonist immediately before docetaxel infusion. Physical examinations and routine laboratory tests were performed at baseline and then repeated at least once every 3 weeks. Tumor assessments were performed at baseline and every 6 weeks according to RECIST. Response had to be reconfirmed at least 4 weeks after first being noted. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events, version 3.0.

STATISTICAL ANALYSIS

The sample size was based on a Simon’s minimax design. The null hypothesis assumed that the response rate was less than 5%, and the alternative hypothesis assumed that the response rate was at least 25%, with a type I error level of 0.05% and a type II error of 0.2%. A total of 16 patients were scheduled to be enrolled.

RESULTS

Between September 2006 and February 2009, a total of seven patients (six men and one woman) were enrolled (Table 1). The median age was 68 years (range, 66–78). No patient had a performance status of 2. Three patients received surgery for their neck tumors, one of whom additionally received radiation therapy of the primary lesion after debulking surgery. The median number of administered treatment cycles was 2 (range, 1–13). The dose of docetaxel was reduced by 25% because of neutropenia in one patient.

Efficacy

Of the seven patients who received docetaxel, one had a complete response, two had stable disease and four had progressive disease for a response rate of 14% and a disease control rate (complete response plus stable disease) of 43%. The median time to progression was 6 weeks (range, 1–50 weeks), and overall survival was 13 weeks (range, 7–104 weeks).

The patient with a complete response had a relapse of multiple lung metastases at baseline (Patient no. 2 in Table 2; Fig. 1). This patient had previously received resection of the primary tumor and post-operative radiotherapy. After seven cycles of treatment with docetaxel, the lung metastases disappeared completely on radiological examinations. The patient received a total of 13 cycles of docetaxel until disease progression was documented 50 weeks after study entry. A diagnosis of ATC was reconfirmed pathologically, and there were no any special findings.

After docetaxel treatment, one patient (Table 2, Patient no. 1) was treated with doxorubicin. The progression was observed after one cycle of the treatment of doxorubicin, and the patient was treated with the best supportive care. Two patients (Table 2, Patient nos 4 and 5) received palliative external beam radiotherapy to selected tumor sites. The other patients were treated with best supportive care.

Toxicity Evaluation

Adverse events associated with docetaxel were assessed in all seven patients. Hematological toxicity was relatively
mild. One patient had Grade 4 neutropenia on day 8 of the first cycle and received granulocyte colony-stimulating factor for 4 days. Blood transfusions were not given to any patient. Non-hematologic toxicity, including peripheral neuropathy and hypersensitivity reactions, was negligible clinically.

Airway obstruction occurred in one patient 3 days after of the first dose of docetaxel (Patient no. 4 in Table 2). Emergent endotracheal intubation with mechanical ventilation support was required before tracheotomy. Although mild edema of the larynx was noted at the time of intubation, the airway obstruction was apparently caused by local growth of the primary tumor, rather than an adverse reaction to docetaxel. On the basis of experience with this patient, the monitoring committee recommended that patients in whom aggressive local therapy was indicated should be excluded from the study.

After seven patients had been enrolled, the study was terminated at the recommendation of the monitoring committee because of slow enrollment.

DISCUSSION

This study showed that docetaxel could be an effective drug for the treatment of ATC, with a response rate of 14% and a disease control rate of 43%. Studies of docetaxel chemotherapy in patients with ATC are scant. In a recent case report, one patient who received docetaxel plus radiation as adjuvant therapy survived for more than 36 months without recurrence (11). In a Phase I study of docetaxel in combination with epirubicin and cyclophosphamide, two of three patients with ATC had partial responses (13). Our results together with these clinical observations suggest that docetaxel is moderately active against ATC, similar to paclitaxel and doxorubicin.

The results of the present study also emphasized the importance of aggressive surgical therapy of local lesions to prevent or palliate upper airway respiratory failure caused by primary tumors. In the one patient with severe airway obstruction in our study, tumor shrinkage in response to docetaxel monotherapy was inadequate to preserve upper airway

Figure 1. Computed tomographic scans of the lungs, taken at the level of the heart at baseline (a) and after seven cycles (b). Multiple lung metastases completely disappeared after chemotherapy.
competency in the neck. Sugino et al. (3) retrospectively reviewed 40 consecutive patients with ATC treated at a single institution and reported that patients who received palliative debulking surgery of their neck tumors survived longer than those who did not. Thus, aggressive local surgical therapy should take precedence over systemic chemotherapy in patients with ATC.

Multiple lung metastases disappeared for 50 weeks in one patient who had a complete response in this study. Interestingly, some patients with ATC have a very good response to chemotherapy, despite the aggressive nature of this lethal disease. One patient with ATC in a Phase II study of paclitaxel (12) and 3 of 18 patients with ATC who received a combination of doxorubicin and cisplatin had complete responses, and 2 of 5 patients with ATC who received a combination of doxorubicin, cisplatin and bleomycin had complete responses in previous studies (6,8). Although patients with ATC seem to be biologically homogenous, a specific subgroup might be very sensitive to chemotherapy. Identification of these ‘super’ responders (if any) might help to define patients with ATC who are most sensitive to chemotherapy.

In conclusion, this study showed that docetaxel could be an effective drug with tolerable toxicity against ATC. Because chemotherapy is of limited value for controlling primary lesions, aggressive local surgical therapy should take precedence over systemic chemotherapy in patients with ATC. Whether combination chemotherapy with docetaxel plus platinum agents such as cisplatin improves response should be evaluated in future clinical trials.

Conflict of interest statement

None declared.

References