Docetaxel for platinum-refractory advanced thymic carcinoma

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Original Article

Abstract

Objective: Thymic carcinoma is a rare mediastinal neoplasm. While platinum-based chemotherapy has been reported to be effective for advanced thymic carcinoma in a first-line setting, little information is available regarding the benefits of salvage chemotherapy for platinum-refractory thymic carcinoma. This study assessed the efficacy and safety profiles of docetaxel monotherapy for platinum-refractory thymic carcinoma.

Methods: A total of 13 thymic carcinoma patients treated with docetaxel monotherapy in a second- or later-line setting between January 2003 and April 2014 were retrospectively reviewed. The median age was 61 years (range, 41–75 years).

Results: The overall response rate and disease control rate were 31% [95% confidence interval (CI), 6–56%] and 77% (95% CI, 54–100%), respectively. The median progression-free survival and overall survival after docetaxel monotherapy were 5.5 months (95% CI, 2.3–6.5 months) and 24.0 months (95% CI, 9.4–31.2 months), respectively. The most common Grade ≥3 toxicity was neutropenia (62%). No incidents of febrile neutropenia and no treatment-related deaths were recorded.

Conclusions: This retrospective analysis demonstrated that docetaxel was active against platinum-refractory thymic carcinoma with acceptable toxicities. Docetaxel monotherapy might be a promising therapeutic option for patients with platinum-refractory thymic carcinoma.

Key words: chemotherapy, docetaxel, platinum, thymic carcinoma

Introduction

Thymic carcinoma (TC) is a rare mediastinal neoplasm with malignant cytologic features and a propensity to undergo capsular invasion and metastasis (1–8). It can be distinguished from thymoma by its biological characteristics and clinical outcome. Compared with thymoma, TC tends to follow a much more aggressive clinical course and is associated with a significantly poorer prognosis. Therefore, TC was classified as a distinct entity from thymoma in the 2004 World Health Organization (WHO) classification (9).

Systemic chemotherapy represents the standard treatment for advanced TC. Although no optimal chemotherapeutic regimen for TC has been established, to date, because of its rarity, several prospective and retrospective studies have repeatedly indicated the efficacy of platinum-based combination chemotherapy as a front-line treatment against TC (10–16). Meanwhile, there have been only a few case reports describing salvage chemotherapy for platinum-refractory TC (17–22).

Docetaxel, a semisynthetic taxane targeting the β-subunit of tubulin, has exhibited clinical activity against a wide variety of malignancies. Regarding its activity against TC, docetaxel in combination with cisplatin as a neoadjuvant chemotherapy resulted in a novel response in patients with TC in a recent prospective Phase II trial (23). Considering this result, docetaxel might be potentially efficacious against TC. However, the efficacy of single-agent docetaxel for platinum-refractory TC has not been investigated.
In this context, we conducted a retrospective analysis of docetaxel monotherapy to evaluate its efficacy and tolerability in platinum-refractory TC.

**Patients and methods**

**Patient selection**

Between January 2003 and April 2014, a total of 49 TC patients were diagnosed at the National Cancer Center Hospital East (Chiba, Japan). Among them, we retrospectively identified patients who satisfied the following criteria: (i) histologically confirmed TC; (ii) underwent docetaxel monotherapy as a second- or later-line chemotherapy and (iii) the existence of measurable targeted lesions using computed tomography. Of the 49 TC patients, 35 patients received some types of chemotherapy with or without thoracic radiotherapy because of local invasion and/or distant metastasis. Among them, 13 patients received docetaxel monotherapy as a second- or later-line treatment. All the clinical and laboratory data were collected retrospectively from the patients’ medical records. Histology was classified according to the WHO classification, and clinical staging was determined according to the Masaoka-Koga staging system (24). Data were collected in accordance with the International Thymic Malignancy Interest Group Standard Definitions and Policies (25). This study was approved by the Institutional Review Board of National Cancer Center Hospital East.

**Treatment method**

Docetaxel was administered on Day 1 via a 60 min intravenous infusion at a dose of 60 mg/m². Treatment cycles were repeated every 3 or 4 weeks. Dose reduction and the discontinuation of chemotherapy were performed at the physician’s discretion. Docetaxel treatment was continued until disease progression, the appearance of unacceptable toxicity or the patient’s refusal.

**Evaluation of response and toxicity**

The objective tumor response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors guidelines, version 1.1. The objective response rate (ORR) was calculated as the total percentage of patients with a complete response (CR) or a partial response (PR). In this study, confirmation of CR and PR were not performed. The disease control rate (DCR) was calculated as the total percentage of patients with CR, PR or stable disease (SD). Toxicity was graded according to the Common Terminology Criteria for Adverse Events version 4.0.

**Statistical analysis**

The median progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method. The OS was calculated from the date of the initiation of docetaxel treatment until the time of death or the last follow-up examination. The PFS was defined as the interval between the initiation of docetaxel and the date of disease progression or death from any cause. Survival was assessed up until 30 November 2014.

**Results**

**Patient characteristics**

The baseline characteristics of the 13 consecutive patients are summarized in Tables 1 and 2. The median age was 61 years (range, 41–75 years). Male patients (62%) and patients with an Eastern Cooperative Oncology Group Performance Status (PS) of 1 (85%) were predominant. According to the Masaoka-Koga staging system, one patient (8%)...
had Stage III disease, five patients (38%) had Stage IVa disease, three patients (23%) had Stage IVb disease and four patients (31%) had postoperative recurrent disease. The histological classifications were squamous cell carcinoma in nine (69%) patients and undifferentiated carcinoma in four (31%) patients. All the patients had previously received platinum-based chemotherapy. The prior chemotherapeutic regimens included cisplatin and gemcitabine (eight patients); cisplatin and vinorelbine (three patients); carboplatin and paclitaxel (one patient) and cisplatin, vincristine, doxorubicin and etoposide (one patient).

**Treatment efficacy and survival**

The median number of cycles administered was 6 (range, 2–13). Among the 13 patients, 4 had PR and 6 had SD, yielding an ORR of 31% [95% confidence interval (CI), 6–56%] and a DCR of 77% (95% CI, 54–100%) (Table 2). At the time of analysis, the median follow-up duration for the surviving patients was 23.0 months (range, 4.3–72.2 months). The median PFS and the median OS of all the patients were 5.5 months (95% CI, 2.3–6.5 months) and 24.0 months (95% CI, 9.4–31.2 months), respectively (Figs 1 and 2).

**Toxicity**

The Grade ≥2 toxicities are summarized in Table 3. Toxicity was evaluated for all the patients. The most common Grade ≥3 adverse event was neutropenia (62%). However, none of the patients developed febrile neutropenia requiring support with granulocyte-colony stimulating factor. In addition, there were no patients with Grade ≥3 anemia or thrombocytopenia. Although the non-hematological toxicities were generally mild, four patients requested treatment interruption because of Grade 2 non-hematological toxicities (anorexia: 1, edema: 1, peripheral neuropathy: 1, rash: 1). All four patients recovered from these non-hematological toxicities after treatment discontinuation. No treatment-related deaths occurred.

**Subsequent treatments after docetaxel monotherapy**

Of the 13 included patients, 10 patients received subsequent chemotherapy after docetaxel monotherapy (Table 4). The median number of subsequent chemotherapy regimens administered was 2 (range, 0–3). Additionally, three patients received palliative thoracic radiotherapy after disease progression.

**Discussion**

In this study, docetaxel monotherapy (60 mg/m² on Day 1 every 3 or 4 weeks) resulted in an ORR of 31% and a median PFS of 5.5 months,
with an acceptable toxicity profile. These results suggest that docetaxel monotherapy for the treatment of platinum-refractory TC is potentially effective.

To date, no optimal chemotherapeutic regimen has been determined for TC because of the insufficiency of randomized prospective trials. However, several prospective and retrospective studies have repeatedly indicated that TC is sensitive to platinum-based chemotherapy, so a platinum-based regimen is currently the standard first-line treatment for advanced TC (10–16). Meanwhile, reports regarding salvage chemotherapy for platinum-refractory TC have been limited to case reports or small case series (17–22). Therefore, the role of salvage chemotherapy for platinum-refractory TC remains unclear.

Docetaxel has been reported to be an active chemotherapeutic agent for advanced TC in a few studies. Recently, Park et al. (23) designed a prospective non-randomized clinical trial treating 27 patients with thymic epithelial tumors (TC: 18 patients, thymoma: 9 patients) with cisplatin plus docetaxel in a neoadjuvant setting. In a subset of TC patients, 12 patients (67%) achieved a PR after three cycles of cisplatin + docetaxel. As for the single-agent use of docetaxel, Oguri et al. (26) reported a case of TC that showed a novel response to docetaxel monotherapy in a second-line setting. To the best of our knowledge, there are no other reports reporting the clinical activity of docetaxel as a single-agent in platinum-refractory TC beyond this previous case report.

The results of the salvage chemotherapies for recurrent TC are summarized in Table 5. The regimens used in the previous studies included irinotecan, amrubicin, S-1 and pemetrexed (17–22). Although a direct comparison between these regimens is not easy because of the small sample size, the treatment efficacy observed in our study is almost comparable with the results of these previous reports.

Compared with the median PFS of 5.5 months, the median OS of 24.0 months was relatively long. The possible explanations for this difference are as follows. First, the relatively long survival period in this study could be attributable to the subsequent treatments performed after docetaxel monotherapy. Several chemotherapeutic agents have been reported to be effective for platinum-refractory TC, and these agents were used after docetaxel monotherapy in our study. Additionally, three patients had received palliative thoracic radiotherapy. These subsequent treatments might have affected the prolongation of survival. Second, the patients who received docetaxel monotherapy in this study represented a selected population with a good PS (0–1).

Regarding the toxicity profile, Grade ≥3 neutropenia frequently developed in this study. However, the frequency (62%) of Grade ≥3 neutropenia observed in this study was consistent with those detected in previous reports of docetaxel monotherapy for other types of cancer (27–29). No incidents of febrile neutropenia or fatal non-hematological toxicities, including interstitial lung disease, occurred in the present series. Thus, we believe that the toxicity profile observed in this study was tolerable as a second- or later-line treatment for platinum-refractory TC.

Several limitations of the current study should be considered. Firstly, this study was a retrospective, non-randomized study performed at a single center. Secondly, our sample size was relatively small, but this is a common limitation of studies examining TC because of the rarity of this disease. Thirdly, the patient population was confined to Japanese patients.

In conclusion, this retrospective analysis demonstrated that docetaxel was active against platinum-refractory TC with acceptable toxicities. Docetaxel monotherapy might be a promising therapeutic option for platinum-refractory TC. Further investigations of this agent for platinum-refractory TC patients are warranted.

**Conflict of interest statement**

None declared.

**References**


**Table 5. Comparison with previous reports examining chemotherapy as a second or later-line treatment for thymic carcinoma**

<table>
<thead>
<tr>
<th>Author (Ref)</th>
<th>N</th>
<th>Regimen</th>
<th>ORR (%)</th>
<th>DCR (%)</th>
<th>mPFS</th>
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</thead>
<tbody>
<tr>
<td>Kanda et al. (17)</td>
<td>7</td>
<td>Irinotecan + Platinum</td>
<td>29</td>
<td>71</td>
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<tr>
<td>Kouzumi et al. (18)</td>
<td>6</td>
<td>Amrubicin + Platinum</td>
<td>33</td>
<td>83</td>
<td>5.0</td>
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<td>Okuma et al. (19)</td>
<td>4</td>
<td>S-1</td>
<td>50</td>
<td>100</td>
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<tr>
<td>Hirai et al. (20)</td>
<td>9</td>
<td>Amrubicin</td>
<td>44</td>
<td>56</td>
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</tr>
<tr>
<td>Hirai et al. (21)</td>
<td>8</td>
<td>S-1 + Gemcitabine</td>
<td>50</td>
<td>88</td>
<td>6.0</td>
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<td>Liang et al. (22)</td>
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<td>Pemetrexed + Carboplatin</td>
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<td>6.5</td>
</tr>
<tr>
<td>Our study</td>
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<td>Docetaxel</td>
<td>31</td>
<td>77</td>
<td>5.5</td>
</tr>
</tbody>
</table>

ORR, objective response rate; DCR, disease control rate; mPFS, median progression-free survival.

[a]The subset for thymic carcinoma.


