Carboplatin plus nanoparticle albumin-bound paclitaxel for the treatment of thymic carcinoma

AKIKO TAKAHASHI, RINTARO NORO, NATSUKI TAKANO, KAKERU HISAKANE, SATOSHI TAKAHASHI, AYA FUKUIZUMI, MIWAKO OMORI, TEPPEI SUGANO, SUSUMU TAKEUCHI, SHINJI NAKAMICHI, AKIHIKO MIYANAGA, YUJI MINEGISHI, KAORU KUBOTA, MASAHIRO SEIKE and AKIHIKO GEMMA

Division of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, Tokyo 113-8603, Japan

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Abstract. Thymic carcinoma is a relatively rare type of malignant tumor. The present retrospective study evaluated the efficacy and safety of carboplatin plus nanoparticle albumin-bound paclitaxel for the treatment of advanced thymic carcinoma. The study included data from 12 patients with advanced thymic carcinoma treated in the Nippon Medical School Hospital (Tokyo, Japan). Response to treatment, patient survival and treatment safety were assessed. The objective response rate was 66.7% (8/12 patients). Disease control was achieved in 11 patients (91.7%). At the median follow-up time of 27.6 months (range, 6.2-75.1 months), the median progression-free survival and median first-line overall survival times were 16.7 months [95% confidence interval (CI), 13.2-37.7] and 14.3 months (95% CI, 4.7-54.6), respectively. There was no occurrence of febrile neutropenia or treatment-related death. The results of the present study showed that carboplatin plus nanoparticle albumin-bound paclitaxel was effective and safe. Therefore, it is a promising chemotherapy regimen for the treatment of advanced thymic carcinoma.

Introduction

Although thymoma and thymic carcinoma are relatively rare types of malignant tumors, they account for most mediastinal tumors in adults globally (1-3). Thymomas are a common primary tumor in the anterior mediastinum, although they are rare (1.5 cases/million). Thymic carcinoma is rarer than thymomas. In 2016, the National Comprehensive Cancer Network Guidelines version 2 (4) recommended six combination chemotherapy regimens, excluding radiotherapy, for patients with unresectable disease (5-7). According to the guidelines, carboplatin plus paclitaxel is the recommended regimen for the treatment of patients with thymic carcinoma, owing to the higher response rate compared with that noted for other regimens. However, there is a lack of data from randomized clinical studies to provide a definite indication for the management of this disease.

Nanoparticle (i.e., 130 nm) albumin-bound paclitaxel (nab-paclitaxel) utilizes the properties of albumin, namely the reversible binding of paclitaxel, the subsequent transportation across the endothelial cells and its concentration in the tumor. Since it does not contain solvents or ethanol, paclitaxel can be administered at higher doses than those recommended without premedication (8). Nab-paclitaxel is used without dissolving alcohol and so would be available for treating patients who were allergic to alcohol. In addition, the safety and efficacy of nab-paclitaxel have been demonstrated in patients with various types of cancer at a range of doses (100-260 mg/m^2) (9-13). The present retrospective study evaluated the efficacy and safety of carboplatin plus nab-paclitaxel for the treatment of advanced thymic carcinoma.

Materials and methods

Patients. The present study was conducted on retrospective data from patients treated between December 2013 and November 2017. The last day for survival confirmation was August 30, 2019. During this period, 12 patients with advanced thymic carcinoma received treatment with carboplatin plus nab-paclitaxel at the Nippon Medical School Hospital (Tokyo, Japan). All patients were treated with carboplatin on day 1 [area under the blood concentration time curve (AUC), 6] plus nab-paclitaxel (100 mg/m^2) on days 1, 8 and 15 in cycles repeated every 3 weeks. The medical records of the patients were retrospectively reviewed. The inclusion criteria were as follows: i) Confirmed diagnosis of thymic carcinoma according to the histopathological criteria proposed by the World Health Organization (2014 version) (14); ii) stage III (a thoracic surgeon had rejected these patients as the tumors had infiltrated major vessels.), IVa or IVb disease according to the Masaoka criteria (15); and iii) recurrence or metastases diagnosed through chest or abdominal computed tomography. There were no exclusion criteria. The protocol of this study was approved by the Institutional Review Board of the Nippon Medical School Hospital (approval no. 30-05-933).

Correspondence to: Dr Rintaro Noro, Division of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, 1-1-5, Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan
E-mail: r-noro@nms.ac.jp

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Evaluation of response to treatment and safety. The Response Evaluation Criteria in Solid Tumors (version 1.1) guidelines (16) were used to evaluate tumor responses, including complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Disease control rate (DCR) was defined as the sum of CR, PR and SD values.

Progression-free survival (PFS) time was defined as the period from the first day of administration of carboplatin plus nab-paclitaxel to the day of documented disease progression or death. Overall survival time was defined as the period from the first day of administration of carboplatin plus nab-paclitaxel to the day of death; patients who remained alive were censored on the date of the last visit. Follow-up time was defined as the median time between the first day of treatment and the day of death or last follow-up visit. Survival curves were plotted using the Kaplan-Meier method.

Safety was assessed according to the Common Terminology Criteria for Adverse Events (version 4.0; nih.gov) (17) of the US National Cancer Institute.

Statistical analysis. Survival curves were plotted using the Kaplan-Meier method and analyzed by the log-rank test. Analyses were performed using GraphPad Prism version 8 (GraphPad Software, Inc.). $P<0.05$ was used to indicate a statistically significant difference.

Results

Patient characteristics. A total of 12 patients were included in the present study (Tables I and SI). Among those patients, 2 underwent a tumor resection. Squamous cell carcinoma was the most common histological type (75.0%). All patients had a performance status of 0-1, and were treated with carboplatin on day 1 (area under the blood concentration time curve, 5-6) plus nab-paclitaxel (100 mg/m^2) on days 1, 8 and 15 in cycles repeated every 3-4 weeks.

Four patients had received prior chemotherapy: Three patients had received paclitaxel (200 mg/m^2) plus carboplatin (AUC, 6) 12 months ago, and one patient had received paclitaxel (200 mg/m^2) plus carboplatin (AUC, 6) 7 months ago, irinotecan (100 mg/m^2) plus cisplatin (30 mg/m^2) (weekly) 6 months ago and docetaxel (60 mg/m^2) 6 months ago.

Table I. Clinicopathological characteristics (n=12).

Characteristic	Value
Sex, n (%)	
Male	7 (58.3)
Female	5 (41.7)
Age, years	
Median (range)	64 (41-73)
Histology	
Squamous cell carcinoma	9 (75.0)
Undifferentiated carcinoma	2 (16.7)
Neuroendocrine carcinoma	1 (8.3)
Clinical stage[a]	
III	2 (16.7)
Iva	3 (25.0)
IVb	5 (41.7)
Postoperative recurrence	2 (16.7)
Prior therapy	
No	8 (66.7)
Chemotherapy	4 (33.3)
Performance status	
0	6 (50.0)
1	6 (50.0)

[a]Clinical stage was defined based on the Masaoka criteria.

Table II. Response to treatment (n=12).

Response	n (%)
Complete response	1 (8.3)
Partial response	7 (58.3)
Stable disease	3 (25.0)
Progressive disease	1 (8.3)
Disease-control rate	11 (91.7)

Response and survival analysis. The median number of treatment cycles was 4 (range, 2-6). The relative dose intensity was 66.7%. Reasons for the reduction of the dose included alcoholic liver injury and nephropathy. Notably, 3 patients received maintenance treatment with nab-paclitaxel.

Treatment response data are shown in Table II. CR, PR and DCR were achieved in 1 patient (8.3%), 7 patients (58.3%) and 11 patients (91.7%), respectively. At the median follow-up time of 27.6 months (range, 6.2-75.1 months), the median PFS time of 12 patients was 16.7 months [95% confidence interval (CI), 13.2-37.7] and the median first-line PFS time of 8 patients was 13.6 months (95% CI, 4.3-42.3) (Fig. 1). The median first-line overall survival time was 14.3 months (95% CI, 4.7-54.6). Three patients remained disease-free for >3 years.

Evaluation of safety. Safety was assessed in all patients. Grade ≥3 hematological adverse events were observed in 7 patients (anemia, n=3; decreased platelet count, n=2; neutropenia, n=2; and hyponatremia, n=1). A grade ≥3 non-hematological adverse event (liver disfunction) was observed in 1 patient. For the 3 patients with prolonged grade 3 anemia, the dosage was reduced to 80% of the initial dose. Neuropathy, febrile neutropenia and treatment-related mortality did not occur in this study (Table III).

Discussion

To the best of our knowledge, the present study is the largest investigation conducted thus far to assess the clinical benefits of carboplatin plus nab-paclitaxel in patients with advanced thymic carcinoma. As thymoma and thymic carcinoma are relatively rare types of malignant tumors, this combination may be an option as a chemotherapy regimen for the treatment of advanced thymic carcinoma.

Table III. Adverse events.

Adverse event	All grades, n	%	Grade ≥3, n	%
Hematological				
Leukopenia	2	16.7	2	16.7
Neutropenia	2	16.7	2	16.7
Anemia	5	41.7	3	25.0
Decreased platelet count	3	25.0	2	16.7
Febrile neutropenia	0	0.0	0	0.0
Hyponatremia	1	8.3	1	8.3
Non-hematological				
Infection	0	0.0	0	0.0
Fever	0	0.0	0	0.0
Hepatic injury	1	8.3	1	8.3
Pneumonitis	1	8.3	0	0.0
Diarrhea	1	8.3	0	0.0
Neuropathy	0	0.0	0	0.0
Febrile neutropenia	0	0.0	0	0.0
Treatment-related mortality	0	0.0	0	0.0

Table IV. Studies of carboplatin plus nab-paclitaxel as salvage chemotherapy in patients with thymic carcinoma.

First author, year	Patient sex	Age, years	Histology	Response	PFS, months	(Refs.)
Makimoto *et al*, 2014	Male	40	Sq	PR	-	(19)
Igawa *et al*, 2015	Male	59	LCNEC	PR	<6	(20)
Zhan *et al*, 2015	Female	63	Sq	PR	<36	(21)
Shima *et al*, 2016	Male	22	Lymphoepithelioma-like	PR	-	(22)
Funaishi *et al*, 2017	Male	78	Sq	PR	10.3	(23)

LCNEC, large-cell neuroendocrine carcinoma; nab-paclitaxel, nanoparticle albumin-bound paclitaxel; PFS, progression-free survival; PR, partial response; Sq, squamous cell carcinoma.

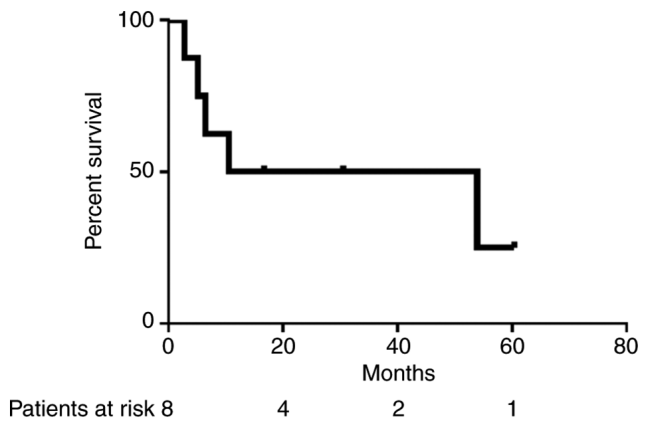

Figure 1. Survival analysis. Progression-free survival for first-line therapy. A total of 3 patients remained disease-free for >3 years.

Lemma *et al* (18) advocated the use of combination chemotherapy consisting of carboplatin plus paclitaxel, in addition to standard therapeutic regimens, for the treatment of advanced thymic carcinoma. Of the 23 patients with thymic carcinoma included in the aforementioned study, 5 patients accomplished a PR, and 12 patients achieved SD (risk ratio, 21.7%; DCR, 73.9%). Notably, the PFS time was 5 months. Table IV shows five case reports of patients with thymic carcinoma who received chemotherapy with carboplatin plus nab-paclitaxel (19-22). These case reports showed that the administration of carboplatin plus nab-paclitaxel resulted in favorable antitumor effects against thymic carcinoma. Funaishi *et al* (23) reported a case with a PFS time of 10.3 months. Ley *et al* (24) and Maurer *et al* (25) suggested the clinical benefit of nab-paclitaxel in recurrent/metastatic gynecological and head and neck carcinomas, which are resistant to paclitaxel and docetaxel. These results are consistent with the present findings, indicating that carboplatin plus nab-paclitaxel may be an option for the treatment of advanced thymic carcinoma. Recently, the efficacy and safety of lenvatinib in patients with advanced or metastatic thymic carcinoma was confirmed in a single-arm, phase 2 trial conducted in eight institutions in Japan (five cancer centers, two medical university hospitals and one public

hospital) (26). In this phase 2 trial, carboplatin and paclitaxel were used as first-line treatment in 71% of cases. The use of lenvatinib after treatment with carboplatin plus nab-paclitaxel was also an effective alternative.

Gong *et al* (27) showed that nab-paclitaxel treatment had a high response rate in non-small cell lung cancer (NSCLC) when used as second-line chemotherapy. No significant difference was found between clinical features and the short-term effect of nab-paclitaxel, such as taxanes, or other second-line chemotherapy. It was also determined that nab-paclitaxel may be an appropriate second-line treatment for patients with thymic cancer who had previously received chemotherapy. Additionally, maintenance monotherapy with nab-paclitaxel may be an option to prolong the PFS time of patients with thymic carcinoma. These results are consistent with those obtained after maintenance monotherapy with nab-paclitaxel for NSCLC (28).

In conclusion, the results presented within the present study suggest that carboplatin plus nab-paclitaxel is a promising salvage chemotherapy regimen for the treatment of advanced thymic carcinoma. Thymic cancer is a very rare type of cancer and the present study contained a limited number of patients as the clinical study was conducted in a single facility. Prospective studies are therefore warranted to further evaluate the efficacy of carboplatin plus nab-paclitaxel chemotherapy for the treatment of thymic carcinoma.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AT, RN, MS, KK and AG were responsible for the conception and design of the study. Provision of study materials or patients, data collection and analysis, and manuscript writing were completed by AT, RN, NT, KH, ST, AF, MO, TS, ST, SN, AM, YM, KK, MS and AG. AT and RN confirm the authenticity of all the raw data. All authors have read and approved the manuscript.

Ethics approval and consent to participate

The protocol of this study was approved by the Institutional Review Board of the Nippon Medical School Hospital (Tokyo, Japan; approval no. 30-05-933).

Patient consent for publication

Not applicable.

Competing interests

RN received honoraria from AstraZeneca and Chugai Pharmaceutical. ST received honoraria for lectures, presentations and speakers bureaus from Taiho Pharmaceutical. YM received payment or honoraria for lectures and presentations from Boehringer Ingelheim Phamaceuticals and Taiho Pharmaceutical. MS received payment or honoraria for lectures and presentations from Boehringer Ingelheim Phamaceuticals, Taiho Pharmaceutical and Eli Lilly Japan K.K. AG received payment or honoraria for lectures and presentations from Boehringer Ingelheim Phamaceuticals. KK received payment or honoraria for lectures and presentations from Chugai Pharmaceutical, Taiho Pharmaceutical, MSD, Nippon Boehringer Ingelheim, Bristol-Myers Squibb, Kyowa-Hakko Kirin, AstraZeneca and Ono Pharmaceutical.

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