Combination Chemotherapy with Doxorubicin, Vincristine, Cyclophosphamide, and Platinum Compounds for Advanced Thymic Carcinoma

Toshihiko Agatsuma, MD,[1] Tomonobu Koizumi, MD, PhD,[2] Shintaro Kanda, MD,[1] Michiko Ito, MD, PhD,[1] Kazuhisa Urushihata, MD,[1] Hiroshi Yamamoto, MD, PhD,[1] Masayuki Hanaoka, MD, PhD,[1] and Keishi Kubo, MD, PhD[1]

[1)] First Department of Internal Medicine, Shinshu University School of Medicine, [2)] Division of Clinical Oncology, Comprehensive Cancer Center, Shinshu University Hospital, Matsumoto, JAPAN

Corresponding author: Tomonobu Koizumi, M.D.

First Department of Internal Medicine, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan

Tel: +81-263-37-2631, **Fax:** +81-263-36-3722

E-mail address: tomonobu@shinshu-u.ac.jp

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ABSTRACT

Introduction: Thymic carcinoma is a rare epithelial neoplasm that tends to be aggressive and metastasize widely. The optimal chemotherapy for unresectable advanced thymic carcinoma has not yet been established because of its rare occurrence. The purpose of the present study was to evaluate the efficacy and tolerability of combination chemotherapy with doxorubicin, vincristine, cyclophosphamide, and platinum compounds for advanced thymic carcinoma.

Methods: A retrospective analysis of 34 untreated and unresectable thymic carcinoma patients who received chemotherapy with doxorubicin, vincristine, cyclophosphamide, and platinum compounds between 1996 and 2010 was conducted. Twenty-nine patients were treated with a combination of cisplatin (50 mg/m^2) and doxorubicin (40 mg/m^2) on day 1, vincristine (0.6 mg/m^2) on day 3, and cyclophosphamide (700 mg/m^2) on day 4. Five patients were treated with carboplatin (area under the curve of 3.0 min mg/mL) instead of cisplatin.

Results: The responses of all 34 patients to the current regimen were assessed. The median number of treatment cycles for the present chemotherapy was 4. The overall response rate and disease control rate were 50.0% and 88.2%, respectively. The median survival was 21.3 months (95% confidence interval [95% CI], 15.0–37.2 months), and

the 1-year and 3-year survival rates were 72.7% (95% CI, 56.8–88.6%) and 34.4% (95% CI, 16.2–52.6%), respectively. The most common adverse event was leukopenia/neutropenia, and non-hematological toxicities were mild.

Conclusions: Combination chemotherapy with doxorubicin, vincristine, cyclophosphamide, and platinum compounds is an effective and well-tolerated treatment for unresectable advanced thymic carcinoma.

Keywords: thymic carcinoma, chemotherapy, platinum

INTRODUCTION

Thymic carcinoma is a rare epithelial neoplasm with malignant cytologic features, and it accounts for approximately 5–36% of all thymic epithelial tumors.[1-3] The clinical course of thymic carcinoma tends to be much more aggressive than that of thymoma, and thymic carcinoma also tends to metastasize widely, which results in poor outcome.[2-7] Therefore, although systemic chemotherapy could play an important role in the treatment of thymic carcinoma, the optimal regimen has not been established because of the rare occurrence of this malignancy. There are few reports describing possible chemotherapy strategies for advanced thymic carcinoma, and these are based on small series and/or retrospective studies.[8-16] These reports have indicated that thymic carcinoma is relatively sensitive to chemotherapy, and cisplatin-based chemotherapies have shown promising results in certain patients with advanced thymic carcinoma. Yoh et al.[12] evaluated the efficacy of CODE (cisplatin, vincristine, doxorubicin, and etoposide) therapy in 12 patients with thymic carcinoma and reported a response rate of 41.7%. Igawa et al.[14] also reported the efficacy of carboplatin plus paclitaxel therapy in 11 patients with a response rate of 36.4%.

Combination chemotherapy with cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC) was initially reported for the treatment of invasive

thymoma. Fornasiero et al.[17] administered ADOC chemotherapy to 37 patients with unresectable invasive thymoma and reported a response rate of 91.8% and a 43% complete remission. Meanwhile, Koizumi et al.[11] described 8 cases with thymic carcinoma treated with ADOC chemotherapy and reported a response rate of 75%. In addition, Kitami et al.[10] reported that all 4 cases who received modified ADOC (nedaplatin, doxorubicin, vincristine, and cyclophosphamide) chemotherapy obtained partial responses.

The present study is a retrospective analysis of 34 unresectable thymic carcinoma patients who received chemotherapy with doxorubicin, vincristine, cyclophosphamide, and platinum compounds in our hospital in the first-line setting. In the present study, the efficacy and the tolerability of this combination chemotherapy for the treatment of advanced thymic carcinoma were assessed.

PATIENTS AND METHODS

A total of 38 consecutive patients with thymic carcinoma were admitted to the Respiratory Division of Shinshu University hospital from August 1996 to March 2010. All patients were histologically diagnosed as thymic carcinoma based on the World Health Organization (WHO) criteria.[18] The histological samples were obtained by percutaneous computed tomography (CT)-guided biopsy, video-assisted thoracic surgery or cervical lymph node biopsy. All patients had local invasion and/or distant metastasis at the time of presentation and were considered to have stage IVa or IVb disease according to Masaoka's classification.[19] Thirty-four out of 38 patients were previously untreated and received systemic chemotherapy as the first-line treatment as described below. A physical examination, complete blood cell count, biochemistry examination, chest radiography, CT scans of the thorax and abdomen, a bone scintigraphy or F-18 fluorodeoxyglucose positron emission tomography (FDG-PET), and magnetic resonance imaging (MRI) scan of the brain were performed for all patients as a pretreatment evaluation. Before the chemotherapy, written informed consent was obtained from all the subjects.

The combination chemotherapy with cisplatin (50 mg/m^2) and doxorubicin (40 mg/m^2) on day 1, vincristine (0.6 mg/m^2) on day 3, and cyclophosphamide (700 mg/m^2)

on day 4, which is termed ADOC chemotherapy, was performed in 29 patients. Five patients were treated with carboplatin (area under the curve of 3.0 min·mg/mL) instead of cisplatin because of insufficient renal function, poor performance status (PS), or advanced age. All drugs were administered intravenously, and dexamethasone (8 mg) and/or granisetron (3 mg) were administered for the prevention of emesis induced by the chemotherapy. This regimen was repeated every 3–4 weeks and continued to the maximum of 6 cycles, if the tumor responded to the treatment and the toxicities were acceptable. Granulocyte colony stimulating factor (G-CSF) was used as treatment for neutropenia but was not used routinely as a prophylactic treatment. Subsequent doses of the anticancer drugs were modified on the basis of hematological and non-hematological toxicities at the discretion of the physician in charge. If the patient's condition allowed it, second-line and further treatments after the current chemotherapy were also performed at the discretion of the attending physician.

The response to chemotherapy was evaluated using the WHO standard response criteria[20] in patients who were treated by 2002 and the Response Evaluation Criteria in Solid Tumors (RECIST)[21] in patients from 2003 onward. The overall survival time was measured from the first day of the treatment with the current combination chemotherapy to the date of death or last follow-up. Fisher's exact test was applied to compare

response rates between cisplatin and carboplatin groups. The survival curves were calculated using the Kaplan–Meier method[22] and compared among responses to the chemotherapy with the log-rank test. A P-value of <0.05 was considered statistically significant. All statistical analyses were performed using MedCalc version 11.4.4 (MedCalc Software, Mariakerke).

Toxicities associated with chemotherapy were graded according to the WHO criteria[23] in patients treated by 1999, the National Cancer Institute - Common Toxicity Criteria (NCI-CTC) version 2.0[24] in patients from 2000 to 2004, and the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0[25] in patients from 2005 onward.

RESULTS

Patient Characteristics

The characteristics of 34 patients are listed in Table 1. Twenty-two patients were men, and 12, women, with median age of 56 years (range, 36–82 years). Twenty-eight patients (82.4%) had PS of 0 or 1 according to the Eastern Cooperative Oncology Group scale.[26] Histological subtypes of thymic carcinoma in the current patients were squamous cell carcinoma in 25 patients (73.5%), small cell carcinoma in 2 patients (5.9%), large cell neuroendocrine carcinoma in 1 patient (2.9%), and undifferentiated carcinoma in 6 patients (17.6%). The diagnoses of the 3 patients with small cell carcinoma or large cell neuroendocrine carcinoma were based on the radiographic and bronchoscopic findings with absence of intrapulmonary and lymph node lesions. Twelve patients (35.3%) had stage IVa disease, and 22 (64.7%), stage IVb disease, according to Masaoka's classification.[19]

Response to chemotherapy and survival

The median number of treatment cycles was 4 (range, 1–6 cycles, Table 1). The responses of the 34 patients to the current chemotherapy are shown in Table 2. Partial response (PR) was achieved in 17 patients, 13 patients showed stable disease (SD), and

only 4 patients demonstrated progressive disease (PD). The overall response rate (RR) and disease control rate (DCR) were 50.0% and 88.2%, respectively. Three patients were treated with radical surgical resection following the current treatment regimen based on favorable tumor reduction in response to chemotherapy.

The median follow-up time was 35.5 months (range, 6.2–96.5 months). Figure 1 shows the overall survival curve for 34 patients. The median survival time (MST) was 21.3 months (95% confidence interval [95% CI], 15.0–37.2 months). The 1- and 3-year survival rates were estimated at 72.7% (95% CI, 56.8–88.6%) and 34.4% (95% CI, 16.2–52.6%), respectively. When the patients were grouped according to the responses to chemotherapy, the MSTs in patients who achieved PR, who demonstrated SD, and who exhibited PD were 25.3 months (95% CI, 11.2–53.0 months), 37.2 months (95% CI, 15.0–111.5 months), and 8.1 months (95% CI, 2.0–23.8 months), respectively (Figure 2). The survival times in the PR and SD groups were significantly superior to those of the PD group (PR vs. PD; P = 0.0197, SD vs. PD; P = 0.0199). There were no statistical differences in the survival times between the PR and SD groups (P = 0.3007).

The RR and DCR in the 29 patients who received cisplatin were 55.2% and 89.7%, respectively. Of the 5 patients who received carboplatin instead of cisplatin, 1 patient achieved PR and 3 exhibited SD. Among the 5 patients, the RR was 20.0% and the

DCR was 80.0%. The survival curves of both groups are shown in Figure 3. The MSTs in cisplatin and carboplatin group were 23.8 months (95% CI, 15.0–47.6 months) and 7.7 months (95% CI, 2.0–32.3 months), respectively. Although the RR, DCR and survival time in the cisplatin group showed a favorable tendency compared with those in the carboplatin group, there were no statistical differences, respectively (RR; P = 0.3328, DCR; P = 0.8945, survival time; P = 0.2000).

Toxicities

The main toxicities of the current chemotherapy in the 34 patients are summarized in Table 3. Grade 3 or 4 leukopenia and neutropenia were observed in 24 patients (70.6%) and 26 patients (76.5%), respectively. There were no patients with grade 3 or more severe anemia. Grade 3 thrombocytopenia was observed in 1 patient (2.9%). Although 4 patients (11.8%) developed febrile neutropenia, they were successfully treated with antibiotics and G-CSF. The most common non-hematological toxicity was anorexia, which was observed in 8 patients (23.5%) with a grade of 3. Grade 3 nausea and vomiting were seen in 7 (20.6%) and 2 patients (5.9%), respectively. Those symptoms improved in a short period after the completion of chemotherapy in most of the patients. Overall, the non-hematological toxicities were regarded as mild. There were no

treatment-related deaths with the current chemotherapy.

DISCUSSION

The present report describes the efficacy and toxicities of combination chemotherapy with doxorubicin, vincristine, cyclophosphamide, and platinum compounds in 34 patients with unresectable advanced thymic carcinoma. Data on chemotherapy regimens for the treatment of advanced thymic carcinoma are very limited, and a standard treatment regimen therefore remains to be established. To the best of our knowledge, the current report is the largest series study analyzing chemotherapy strategies for thymic carcinoma.

With regard to studies on >10 thymic carcinoma patients to evaluate the efficacy of a single regimen, there are currently only 2 retrospective reports.[12,14] A study evaluating CODE chemotherapy in 12 patients reported a RR of 41.7% and MST of 46 months,[12] and in another study, combination chemotherapy with carboplatin plus paclitaxel in 11 patients had a RR of 36.4% and MST of 22.7 months.[14] There are no published prospective studies designed exclusively for thymic carcinoma patients, and only 2 reports addressing thymic tumors (thymoma and thymic carcinoma) are available in the current literature.[15,16] In addition, the 2 existing reports included a small number of thymic carcinoma patients (7 and 8 patients, respectively). Therefore, the evaluation of chemotherapy for advanced thymic carcinoma based on previous reports is difficult. In

the current study, combination chemotherapy with doxorubicin, vincristine, cyclophosphamide, and platinum compounds in 34 patients with advanced thymic carcinoma demonstrated a RR of 50.0%. This result could be equivalent or superior to CODE chemotherapy[12] and to carboplatin plus paclitaxel chemotherapy.[14] While the MST in CODE chemotherapy was reported to be 46 months,[12] the MST in the present study was 21.3 months. This difference might be partly due to the predominance of patients with stage IVb disease in our study.

Four patients exhibited PD in the current study. After the completion of the chemotherapy series, 2 patients received the best supportive care because of a deterioration of PS. Sequential radiation was given to 2 other patients after PD, and only 1 patient achieved PR as best response. Besides, these 2 patients received other chemotherapies after the radiotherapy but could not achieve PR in any regimens. Based on these results, thymic carcinoma showing resistance to the current chemotherapy regimen may also show resistance against other chemotherapies. Thus the poor response to chemotherapy with doxorubicin, vincristine, cyclophosphamide, and platinum compounds might be predictive of reduced chemosensitivity in patients with advanced thymic carcinoma.

Five patients who received carboplatin instead of cisplatin showed a relatively lower

RR and shorter MST, compared with patients treated with cisplatin. The median age of the patients in the carboplatin group was 79 years (range, 71–82 years). Two patients had a PS of 2, and 4 patients had stage IVb disease. These factors might influence the RR and MST, which could explain the differences observed between the 2 groups. In addition, due to the small number of patients, a comparison between the efficacy of carboplatin and cisplatin is not possible. Differences in the anticancer activity of these 2 agents in thymic carcinoma need to be investigated further.

With regard to adverse events, although the current regimen showed mild gastrointestinal toxicity, leukopenia and neutropenia were frequently seen. In a study of the efficacy of ADOC chemotherapy in 37 invasive thymoma patients reported by Fornasiero et al.,[17] 70% of patients developed grade 3 nausea/vomiting according to WHO criteria,[23] with 22% of patients showing grade 3 leukopenia. These results were regarded as opposite to the present results. The differences in gastrointestinal toxicities might be due to differences in the administration of antiemetics, e.g. steroids and 5-hydroxytryptamine 3 receptor antagonists. The differences in hematological toxicities might be related to the age of the patients; the median age in the present study was 56 years, and in the study by Fornasiero et al.,[17] it was 40 years. In the present study, although leukopenia/neutropenia was the most common adverse event, febrile

neutropenia was observed in as few as 11.8%, and there were no treatment-related deaths. The present treatment therefore proved to be a well-tolerated chemotherapy regimen.

Meanwhile, it is the age of personalized medicine in the treatment strategies for advanced malignancies today. Targeted therapies for the treatment of thymic carcinoma have been described in some case reports and small case series.[27,28] Successful treatments with sorafenib[29,30] and sunitinib[31] for the patients with chemotherapy-resistant advanced thymic carcinoma have been reported, and a phase II study evaluating the combination of cetuximab with chemotherapy is ongoing in patients with thymoma. Thus the combination of the current regimen with these molecular targeted agents may bring further benefit to patients with advanced thymic carcinoma. On the other hand, predictive molecular markers in the treatment for thymic carcinoma should also be examined.

In conclusion, combination chemotherapy with doxorubicin, vincristine, cyclophosphamide, and platinum compounds is a promising treatment strategy for unresectable advanced thymic carcinoma and can be considered an effective regimen for this condition. However, similarly to the previous reports,[10,11] the present report is also based on a retrospective study, and a definitive conclusion can only be reached

through prospective studies. Due to the low incidence rates of this type of carcinoma, the results of the present study indicate that multicenter clinical trials of this chemotherapy for unresectable advanced thymic carcinoma are warranted.

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Total number of patients	34
Gender	
Male	22
Female	12
Age (years)	
Median	56
Range	36–82
Performance status (ECOG)	
0	23
1	5
2	6
Histological subtype	
Squamous cell carcinoma	25
Small cell carcinoma	2
LCNEC	1
Undifferentiated carcinoma	6
Clinical stage (Masaoka)	
IVa	12
IVb	22
Cycles of the current therapy delivered	
Median	4
Range	1–6

Table 1. Patient characteristics. ECOG, Eastern Cooperative Oncology Group; LCNEC, large cell neuroendocrine carcinoma.

	Number of patients	%
Complete response	0	0
Partial response	17	50.0
Stable disease	13	38.2
Progressive disease	4	11.8

Table 2. Responses to chemotherapy with doxorubicin, vincristine, cyclophosphamide, and platinum compounds.

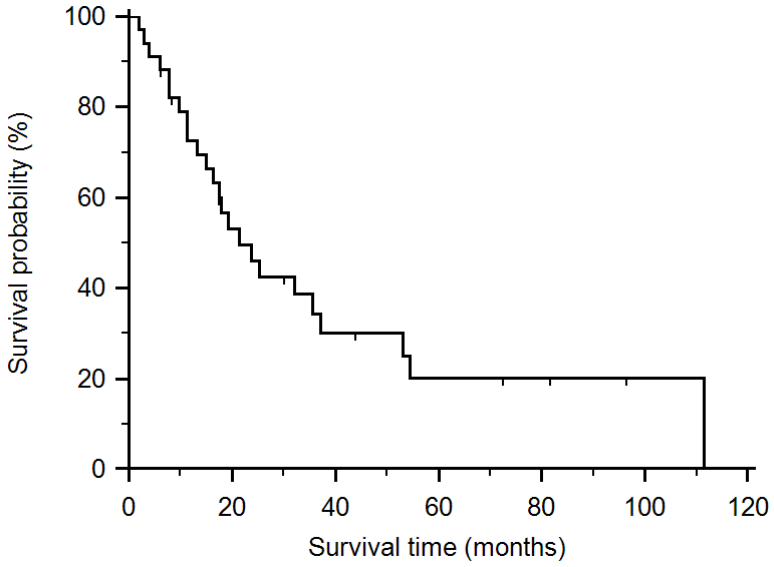

Figure 1. Overall survival curve for the 34 patients included in the study. The median survival time was 21.3 months.

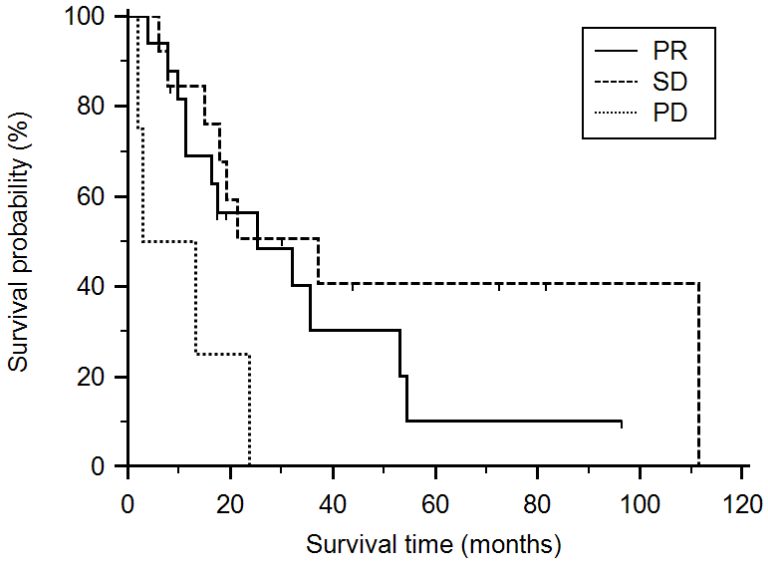

Figure 2. Comparison among survival curves of patients who demonstrated PR, SD, and PD. There were significant differences between PR and PD (P = 0.0197) and between SD and PD (P = 0.0199). PR, partial response; SD, stable disease; PD, progressive disease.

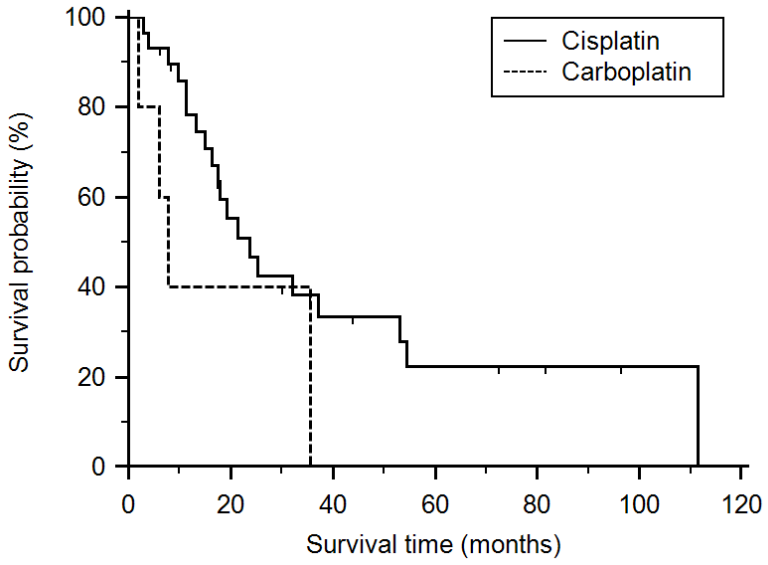

Figure 3. Comparison among survival curves of patients who received cisplatin and carboplatin. There was no significant difference between the cisplatin and carboplatin groups (P = 0.2000).