Response to Cytotoxic Chemotherapy in Patients Previously Treated With Palliative-Intent Chemotherapy for Advanced Thymic Carcinoma

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Abstract

We retrospectively investigated the outcome of chemotherapy in 23 patients with refractory thymic carcinoma because there are few published data concerning this. The response rates to second-, third-, and fourth-line chemotherapy were 39.1%, 23.1%, and 25.0%, respectively, and the median survival time was 18.8 months. Single agents can be beneficial as second- or later-lines of chemotherapy for thymic carcinoma.

Background: Clinical efficacy of second- and later-line chemotherapy for patients with thymic carcinoma previously treated with chemotherapy remains uncertain; limited data are available about this carcinoma because of its rarity. The aim of this study was to investigate effective chemotherapy for patients with thymic carcinoma previously treated with chemotherapy using a retrospective analysis of responses and times to event. **Patients and Methods:** We conducted a retrospective review of the medical records of 23 advanced thymic carcinoma patients previously treated with palliative-intent chemotherapy between 1980 and 2014 in our institution. Clinical demographic characteristics, agents, response, and time to treatment failure for each treatment line and overall survival were reviewed. Factors expected to be associated with survival rates were analyzed. Differences in survival were assessed using Kaplan–Meier analysis and univariate and multivariate Cox proportional hazards regression analyses. **Results:** The study included 13 men (56.5%) and 10 women (43.5%). The median age at diagnosis was 58.5 years. The most common histological subtypes were squamous cell carcinoma (16 patients [69.6%]), followed by neuroendocrine carcinoma (4 patients [17.4%]). The objective response rates of first-, second-, third-, and fourth-line chemotherapy were 60.9%, 39.1%, 23.1%, and 25.0%, respectively. The median survival time was 18.8 months (95% confidence interval, 7.5-40.9 months). Uni- and multivariate analyses of all assessed variables failed to identify any statistically significant indicators of overall survival. **Conclusion:** Patients with thymic carcinoma previously treated with palliative-intent chemotherapy might respond to second- or later-lines of cytotoxic chemotherapy.

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Introduction

Thymoma and thymic carcinoma are categorized as rare cancers according to the definition of the RARECARE project supported by the European Commission.[1] The annual incidence of these thymic malignancies is approximately 0.15 cases in the United States[2] and 0.32 cases in the Netherlands[3] per 100,000 person-years. Thymic carcinoma accounts for less than 1% to 4% of cases of thymic malignancies. It is now believed to be different from thymoma based on biological characteristics, clinical prognosis, and genomic differences measured using the next-generation sequence.

Compared with thymoma, thymic carcinoma has a reportedly worse prognosis and displays more aggressive clinical features due to the loss of thymic function with a high level of atypia. With the loss

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of thymic functions, CD4/CD8 double positive T-cells do not develop, and therefore paraneoplastic complications are generally absent in thymic carcinoma.[4,5] Treatments for patients in advanced stages of thymic carcinoma include palliative-intent chemotherapy or best supportive care. The evidence in support of chemotherapy is insufficient, including only a few retrospective studies based on small groups or studies that are subgroups of single-arm phase II studies.[6,7] Therefore, the selection of active agents for and the benefits of later-lines of chemotherapy for the patients who have undergone first-line chemotherapy for advanced thymic carcinoma remains controversial.[8,9] According to the National Comprehensive Cancer Network (NCCN) guidelines, single-agent chemotherapy is recommended for second- or later-line chemotherapy in thymoma.[8,10] Most of the developments in chemotherapy are commonly based on rare cancers that have been studied prospectively. Recent investigations on molecular targeted agents for c-KIT-positive thymic carcinoma demonstrated moderate efficacies although these mutations are rare in thymic carcinoma (< 10%).[11-15] Recent results of molecular targeted agents for refractory thymic carcinoma are emerging; however, the benefits of later-lines of cytotoxic chemotherapy in such cases remain uncertain.

The objective of the present study was to retrospectively evaluate the clinical benefits of cytotoxic chemotherapy for refractory thymic carcinoma patients treated in our institution.

Patients and Methods

Database and Data Acquisition

We retrospectively reviewed data on patients with a histological or cytological diagnosis of advanced (Masaoka–Koga stage IVa or IVb) or postsurgical recurrent thymic carcinoma who were treated with palliative-intent chemotherapy at the Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital (Tokyo, Japan) between January 1980 and June 2014. We acquired clinical data of patients treated with 2 or more lines of chemotherapy. We used the codes from the International Classification of Diseases (9th edition) to identify the relevant patients from the database. This retrospective study was approved by the Ethics Committee of the Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital (#1467), and conducted in accordance with the Declaration of Helsinki.

A retrospective review of relevant clinical features and treatment-related data of 23 patients who underwent second- or later-lines of chemotherapy with diagnoses of advanced or recurrent thymic carcinoma was performed. The pathological diagnosis was reviewed by a thoracic pathologist (TH) according to the 2004 World Health Organization (WHO) classification[16] and the Masaoka–Koga staging system.[17] Diagnoses of thymic carcinoma were confirmed using hematoxylin and eosin staining and immunohistochemistry for CD5, CD117 (c-KIT), and/or p63 to exclude other malignant thoracic tumors, and supplemental testing for terminal deoxynucleotidyl transferase to distinguish carcinomas from thymomas.

The clinical factors retrieved include the following: (1) patient demographic characteristics including age, sex, Eastern Cooperative Oncology Group Performance Status at first-line chemotherapy, clinical stage according to the Masaoka–Koga staging system at diagnosis, histological type according to the 2004 WHO classification, and previous treatment; (2) type of chemotherapeutic agent used in all lines; (3) best objective response rate for each line of chemotherapy; and (4) survival data. Data were investigated in accordance with the International Thymic Malignancy Interest Group (ITMIG) Standard Definitions and Policies.[18] Survival time was defined as the period from the date of second-line chemotherapy to the date of death from any cause or last follow-up. Progression-free survival was defined as the period from the date of each line of chemotherapy to the date of clinical progression of the disease, the last date of treatment, last follow-up, or death. The best objective responses for all computed tomography scans were assessed using the Response Evaluation Criteria in Solid Tumors criteria version 1.1 for each line of chemotherapy. Correlation between these data and clinical intervention and confirmation of the response was not required because of the retrospective nature of the data.

Statistical Analysis

Descriptive statistics were used to summarize the patient baseline characteristics. Patients who failed to attend for follow-up were censored at the time of last contact. The Fisher exact test or χ^2 test was used to examine the association between 2 categorical variables. Factors predicting survival after second- and later-line chemotherapy were analyzed using univariate and multivariate analyses with the Cox proportional hazards model. The variables examined included age (< 70 vs. ≥ 70 years), sex (male vs. female), clinical stage (IVa/IVb vs. recurrence), and histological subtype (low-grade vs. high-grade). Low-grade (squamous cell, mucoepidermoid, and basaloid carcinomas) and high-grade (lymphoepithelioma-like, neuroendocrine, clear cell, sarcomatoid, and undifferentiated carcinomas) tumors were defined according to the definitions provided by Suster and Rosai.[19] Differences were considered to be significant at $P < .05$.

All statistical analyses were performed using JMP9 (SAS Institute, Cary, NC).

Results

Characteristics of Advanced Thymic Carcinoma Patients and Their Tumors

A total of 23 patients (13 male, 10 female) treated with palliative-intent chemotherapy for refractory thymic carcinoma were included in this study. Their median age was 58.5 years (range, 14-83 years). An average of 3.70 lines of chemotherapy were administered. At initial diagnosis, thymic carcinoma had metastasized to the lungs, liver, and bones. At diagnosis, 5 patients (21.7%) had stage IVa disease, 15 patients (65.2%) had stage IVb disease, and 3 patients had recurrent disease (13.0%). Histologic examination revealed 7 subtypes of thymic carcinoma: 16 patients (69.5%) had squamous cell carcinoma, 4 patients (17.4%) had neuroendocrine carcinoma (1 had small cell carcinoma, 2 had large cell neuroendocrine carcinoma, and 1 had carcinoid carcinoma), 1 patient had mucoepidermoid carcinoma, 1 patient had undifferentiated carcinoma, and 1 patient had lymphoepithelioma-like carcinoma. No autoimmune complications were observed. Patient characteristics are shown in Table 1; regimens of first-line chemotherapy are shown in Table 2. Most patients were treated with platinum-based chemotherapy; 19 (82.6%) received cisplatin-based and 2 received carboplatin-based chemotherapy. The response rate of first-line chemotherapy was