Lung Cancer 80 (2013) 75–80

Contents lists available at SciVerse ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Clinical outcomes with chemotherapy for advanced thymic carcinoma

Yusuke Okuma[a,*], Yukio Hosomi[a], Yusuke Takagi[a], Eisaku Sasaki[b], Tsunekazu Hishima[c], Yoshiharu Maeda[b], Masahiko Shibuya[a], Tatsuru Okamura[a]

[a] Department of Thoracic Oncology and Respiratory Medicine, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, 3-18-22 Honkomagome, Bunkyo, Tokyo 113-8677, Japan
[b] Department of Chemotherapy, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, 3-18-22 Honkomagome, Bunkyo, Tokyo 113-8677, Japan
[c] Department of Pathology, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, 3-18-22 Honkomagome, Bunkyo, Tokyo 113-8677, Japan

ARTICLE INFO

Article history:
Received 10 September 2012
Received in revised form 2 December 2012
Accepted 5 December 2012

Keywords:
Thymic carcinoma
Prognostic significance
Chemotherapy
Metastasis
Thymic epithelial neoplasm

ABSTRACT

Background: The clinical characteristics and prognostic factors of thymic carcinoma have not been investigated in detail because of its rarity. The aim of this study was to elucidate the disease profile, outcomes, and prognostic factors for survival among patients with advanced thymic carcinoma treated with palliative-intent chemotherapy.
Patients and methods: A retrospective review was conducted of the medical records of 40 patients treated with palliative-intent chemotherapy for advanced thymic carcinoma between 1991 and 2011 in our institution. Clinical demographics, histology, overall survival, and factors expected to predict survival were analyzed. Differences in survival were assessed using Kaplan–Meier analysis and univariate and multivariate Cox proportional hazards regression analyses.
Results: The study included 22 males (55.0%) and 18 females (45.0%). The median age at diagnosis was 58.5 years. The most common metastatic sites at diagnosis were lung (45.0%), lymph nodes (20.0%), liver (15.0%), bone (15.0%), and brain (5.0%). The most common histological subtypes were squamous cell carcinoma (70.0%), followed by neuroendocrine carcinoma (17.5%), and mucoepidermoid carcinoma (7.5%). The response rate for first-line chemotherapy was 47.5%. The median survival time was 24.5 months (95% confidence interval 20.9-43.5 months). Overall survival rates at 1-, 2-, and 5-years were 72.5%, 52.5%, and 17.5%, respectively. In uni- and multivariate analyses, the only favorable prognostic factor for overall survival was response to first-line chemotherapy ($p = 0.01$).
Conclusion: Response to first-line chemotherapy may be implicated as a potential surrogate for survival in advanced thymic carcinoma.

1. Introduction

Thymic epithelial neoplasm (TEN) is a rare cancer comprising thymoma, thymic carcinoma, and thymic neuroendocrine carcinoma; it has an annual incidence of 0.15 per 100,000 person-years [1]. The European Union defines a rare cancer as any cancer with an incidence of less than 6 per 100,000 persons per year; thus, based on these criteria, TEN is considered a rare disease and thymic carcinoma accounts for less than 1-4% of cases of TEN. Thymic carcinoma is definitively distinguished from thymoma based on biological characteristics and clinical prognosis. However, it is difficult to fully understand the clinical characteristics and prognostic factors among patients with advanced thymic carcinoma because of its rarity. Thymic carcinoma does not preserve the cortex or medulla of the thymus, therefore, causing the loss of thymic function. In contrast, thymoma induces the development of CD4+/CD8+ double positive T-cells. Thus, paraneoplastic syndromes induced by autoantibodies, such as myasthenia gravis, pure red cell aplasia, or hypogammaglobulinemia, do not occur in thymic carcinoma [2,3]. No overt symptoms appear during the early stage; rather, the initial symptoms tend to occur with tumor extension or metastasis. Therefore, thymic carcinoma is usually diagnosed after extension with poor prognosis. Patients in the advanced stages of thymic carcinoma (Masaoka–Koga stage IVa, IVb, or recurrent disease) are usually treated with palliative-intent chemotherapy or best supportive care. Patients with stage IVa disease have been shown to experience prolonged survival with multimodality treatment in combination with curative-intent surgery, radiotherapy, and chemotherapy [4]. Wekslter et al. demonstrated the survival benefit with surgical intervention [5]. There is only a low level of evidence in support of chemotherapy, with a few retrospective studies based on small groups of treated patients with diverse backgrounds are available; thus, the optimal therapeutic strategy remains controversial. The rarity of this orphan tumor has

* Corresponding author. Tel.: +81 03 3823 2101; fax: +81 03 3824 1552.
E-mail address: y-okuma@cick.jp (Y. Okuma).

0169-5002/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.lungcan.2012.12.012

precluded it from undergoing prospective studies. When limited to thymic carcinoma, Lemma et al. showed a moderate response to carboplatin and paclitaxel in a phase II trial [6]. Other prospective clinical trials have provided evidence on the efficacy of chemotherapy for only thymoma. Overall, the prognosis and prognostic factors have not been well investigated in advanced thymic carcinoma.

The objective of the present study was to retrospectively evaluate the clinical characteristics, prognosis, and prognostic factors of thymic carcinoma among patients with advanced thymic carcinoma treated with palliative-intent chemotherapy in our institution.

2. Patients and methods

2.1. Database

Patients treated with palliative-intent chemotherapy for advanced thymic carcinoma were identified from the databases at Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital (Tokyo, Japan) between January 1, 1991 and December 31, 2011. Codes were used from the International Classification of Diseases (9th edition). This study was approved by the institutional review board.

2.2. Data acquisition

A retrospective review was performed to collect data on the outcomes of 40 consecutive patients treated with chemotherapy for thymic carcinoma of Masaoka–Koga stage IVa, IVb, or recurrent disease. Thymic carcinoma was confirmed by hematoxylin–eosin staining and immunohistochemistry using CD5 and/or CD117 (c-KIT) to exclude other malignant thoracic tumors, and/or terminal deoxynucleotidyl transferase (TdT) to distinguish from thymoma at initial diagnosis. The pathological review was performed consistently by a specialist in thymic malignancies. Individuals with a histological diagnosis of thymoma were excluded. Recurrent disease was defined as disease that was not responsive to curative-intent treatment; all patients with recurrent disease were chemonaïve and underwent palliative-intent chemotherapy. Recurrent disease was determined by chest computed tomography, magnetic resonance imaging, positron emission tomography, or bone scanning. Histology was also classified according to the WHO classification, and staging was determined by the Masaoka–Koga staging system. We also examined such clinical factors as age, staging, Eastern Cooperative Oncology Group Performance Status, cigarette smoking, initial symptoms at diagnosis, metastasis to distant organs, histology, treatment modality, response to first-line chemotherapy as defined by radiographic images, number of later lines of chemotherapy, and survival. In terms of histology, we analyzed survival according to low-grade histology (squamous cell carcinoma, mucoepidermoid carcinoma, and basaloid carcinoma) and high-grade histology (lymphoepithelioma-like carcinoma, neuroendocrine carcinoma, clear cell carcinoma, sarcomatoid carcinoma, and undifferentiated carcinoma) as defined by Suster and Rosai [7]. Data were collected in accordance with the International Thymic Malignancy Interest Group (ITMIG) Standard Definitions and Policies [4]. The medical records and laboratory data for each patient were retrieved for analysis and assessment of treatments for thymic carcinoma. In patients with stage IVa disease, survival time was defined as the length of time from the day when the patient began first-line palliative-intent chemotherapy (excluding the adjuvant setting if the patient underwent surgery) to the day of death. Patients were treated with palliative-intent chemotherapy, with or without a combination of radiotherapy in the first-line setting. A "responder" was defined as a patient who achieved complete response or partial response as assessed by the Response Evaluation Criteria in Solid Tumors criteria version 1.1 (RECIST 1.1) with first-line chemotherapy. A "non-responder" was defined as a patient with stable disease or progressive disease.

2.3. Statistical analysis

The primary end point was the association between several prognostic factors and overall survival. Survival time was defined as the period from the date of initiation of first-line chemotherapy to the date of death from any cause or last follow-up using the Kaplan–Meier method. Patients lost to follow-up were censored at the time of last contact. Due to the retrospective nature of the data, these relevant end points were chosen to reflect clinical practice.

The Kaplan–Meier method was used to estimate overall survival, 1-year, 2-year, and 5-year survival. The log-rank test was used to identify prognostic factors for survival in the univariate analysis. Variables analyzed included age (<65 vs. ≥65 years), gender (male vs. female), histology (low-grade vs. high-grade), disease stage (IVa vs. IVb vs. recurrent), serum lactate dehydrogenase (LDH) level at diagnosis (<200 IU/dL vs. ≥200 IU/dL), and response to first-line chemotherapy (responder vs. non-responder) in uni- and multivariate analyses. Significant factors ($p < 0.05$) in univariate analysis were included in the multivariate Cox proportional hazards model. All statistical analyses were performed using SAS (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics

A total of 40 patients (22 males, 18 females) were treated with palliative-intent chemotherapy for advanced thymic carcinoma. Their median age was 58.5 years (range, 14–83 years). At initial diagnosis, thymic carcinoma had metastasized to the lungs, liver, and bone. At diagnosis, 10 patients (25.0%) had stage IVa disease, 22 patients (55.0%) had stage IVb disease, and 8 patients had recurrent disease (20.0%). Histologic examination revealed 6 subtypes of thymic carcinoma: 28 patients had squamous cell carcinoma (70.0%), 7 patients (17.5%) had neuroendocrine carcinoma (3 patients had small cell carcinoma, 2 patients had large cell neuroendocrine carcinoma, and 2 patients had carcinoid), 3 patients had mucoepidermoid carcinoma (7.5%), and 1 patient had lymphepithelioma-like carcinoma. No patients complicated by autoimmune-related symptoms were observed. Patient characteristics are shown in Table 1.

3.2. Outcome of chemotherapy and factors affecting survival

The types of first-line chemotherapy administered are also shown in Table 1. For first-line chemotherapy, 11 patients (27.5%) received ADOC, consisting of cisplatin, adriamycin, vincristine, and cyclophosphamide; 10 patients (25.0%) received IP, consisting of irinotecan and cisplatin; 12 patients (30.0%) received other cisplatin-containing regimens; 3 patients (7.5%) received carboplatin-based doublets chemotherapy; and 4 patients (10.0%) received single agent or non-platinum-based therapy. Disease control was observed in 31 patients (77.5%), with 19 showing partial responses (47.5%) and 12 showing stable disease (30.0%); 9 patients (22.5%) had progressive disease. There were no complete responders. The response rate for patients treated with cisplatin-containing chemotherapy ($n = 33$) was 51.5%, and the response rate for cisplatin and anthracycline-containing chemotherapy ($n = 11$) was 36.3%. The response rate for platinum-based doublet chemotherapy with a third generation agent ($n = 14$) was 50.0%. The median survival time for all patients was 24.5 months (95%