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Persistent and Aggressive Treatment for Thymic Carcinoma

Results of a Single-Institute Experience with 25 Patients

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Key Words
Thymic carcinoma · Surgery · Radiotherapy · Chemotherapy, systemic

Abstract
Objectives: The aim of this study is to retrospectively evaluate the role of several therapies, mainly chemotherapy, for thymic carcinoma (TC). ***Methods:*** From July 1973 to July 2005, 25 patients (15 males and 10 females) with histologically proven TC were treated at our department. The median age of the patients was 59 years, with a range of from 30 to 78 years. According to Masaoka's staging system, there was 1 stage I patient, 3 stage II, 7 stage III, 6 stage IVa, and 8 stage IVb patients. The histological subtype was in all cases squamous cell carcinoma, nonkeratinizing type. ***Results:*** There were 6 complete surgical resections, 1 incomplete resection followed by chemoradiotherapy, 6 with radiotherapy alone, 3 with radiotherapy plus chemotherapy, and 9 with chemotherapy alone as the initial treatment. Eighteen patients were administered second-line therapy. The regimen obtaining the best response rate was doublet chemotherapy consisting of carboplatin (CBDCA) and paclitaxel. The median survival time and survival rate at 5 years for the patients excluding surgical cases with stage I/II disease were 32 months and 31%, respectively. ***Conclusion:*** The doublet of CBDCA and paclitaxel thus appears to be a promising regimen for TC and further investigation in a multi-institutional phase II trial is, therefore, strongly called for.

Introduction

Thymic carcinoma (TC) is a rare epithelial neoplasm of the thymus that differs from thymoma in its morphological and biological features. Kondo and Monden [1] reported 186 patients (14%) with TC among the compiled records of 1,320 patients with thymic epithelial tumors who were treated from 1990 to 1994 at 115 institutes certified as special institutes for general thoracic surgery by the Japanese Association for Chest Surgery. Most cases occur at middle age (mean age: 57.9 ± 13.2 years), and the male to female ratio was 1.52 (111 men and 73 women). In general, TC is characterized by extensive local invasion and distant metastasis, an aggressive course and a poor prognosis. According to the World Health Organization (WHO) classification of the tumors, TCs are classified as squamous cell carcinoma, basaloid carcinoma, mucoepidermoid carcinoma, lymphoepithelioma-like

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Table 1. Clinicopathological characteristics of the patients

Parameter	n	%
Median age, years	59 (30–78)	
Gender		
Male	15	60
Female	10	40
Histological type		
Squamous cell carcinoma	25	100
Stage		
I	1	4
II	3	12
III	7	28
IVa	6	24
IVb	8	32

Values in parentheses represent range.

Table 2. Initial treatment for TC

Therapy	n	%
Surgery only	4	16
Surgery + adjuvant therapy	3	12
Radiotherapy only	6	24
Radiotherapy + chemotherapy	3	12
Chemotherapy alone	9	36

carcinoma, sarcomatoid carcinoma (carcinosarcoma), clear cell carcinoma, adenocarcinoma, papillary adenocarcinoma, carcinoma with t(15;19) translocation, and undifferentiated carcinoma [2]. Whereas the clinicopathological features of TC have often been discussed, information about the optimal treatment modalities and long-term prognosis is limited due to the rarity of this disease. We retrospectively reviewed 25 cases of TC treated with various modalities and followed them long-term, while also discussing the overall management of this disease.

Material and Methods

Patients and Methods

From July 1973 to July 2005, 25 patients with histologically proven TC were treated at the Department of Thoracic Oncology, Kyushu Cancer Center. We excluded any thymic neuroendocrine tumors in this retrospective study, because their clinical behavior differs from that of the others. The clinical or pathological stage of the disease was based on the staging system described by Masaoka et al. [3]. The histological analysis of the tumor was based on the WHO classification of cell types [2]. Percutaneous biopsy was performed in the cases without a surgical resection to determine the pathological classification. The cases diagnosed before the establishment of the Masaoka criteria or WHO classification were reevaluated by two independent reviewers or pathologists. The clinicopathological characteristics of the patients are shown in table 1. All patients had a good performance status except for performance status 2 due to the superior vena cava syndrome in only 1 patient.

Treatment

The initial therapies are summarized in table 2. A complete resection as the initial therapy was performed in 6 patients, which included 1 patient who received postoperative radiotherapy and 1 postoperative chemotherapy. One patient had an incomplete resection followed by chemoradiotherapy, radiotherapy alone in 6, radiotherapy plus chemotherapy in 3, and chemotherapy alone in 9 as the initial treatment. Nine of the patients with unresectable tumors were treated with irradiation of from 40.0 to 61.2 Gy to the primary tumors. Eighteen patients were administered second-line therapy (chemotherapy in 10, radiotherapy in 4, chemoradiotherapy in 3 and surgical resection followed by radiotherapy in 1), while 12 received third-line (radiotherapy in 6, chemotherapy in 3, chemoradiotherapy, surgical resection and other treatment in 1 each), 10 had fourth-line (radiotherapy in 5, chemotherapy in 2, chemoradiotherapy in 2 and surgical resection followed by chemotherapy in 1), 4 had fifth-line (chemotherapy and radiotherapy in 2 each), 3 had sixth-line (surgical resection, radiotherapy and chemotherapy in 1 each) and 2 had seventh-line treatment (radiotherapy in 2) after the failure of the initial treatment. Several chemotherapy regimens were used, and the results of the first- or second-line chemotherapy for at least 4 patients are summarized in table 3.

Tumor Assessment during and after Treatment

The measurability of target lesions at baseline and the response criteria was based on the Response Evaluation Criteria in Solid Tumours (RECIST) [4]. In brief, lesions that can be accurately measured in at least one dimension as $\geq$20 mm with conventional techniques or as $\geq$10 mm with a spiral CT scan were defined as measurable lesions. The response criteria were categorized as follows: complete response: the disappearance of all target lesions; partial response: at least a 30% decrease in the sum of the pleural thickness at three separate levels; progressive disease: at least a 20% increase in the sum of the pleural thickness at three separate levels or the appearance of one or more new lesions; stable disease: neither sufficient shrinkage to qualify for partial response nor a sufficient increase to qualify for progressive disease. The cases diagnosed before establishment of the RECIST criteria were reevaluated by two independent reviewers of our department.

Statistical Analysis

The duration of stable disease was measured from the start of the treatment until the criteria for disease progression was met. The survival was calculated from the date of the initial treatment until death due to any cause or the last follow-up (censored). The survival curve was made using the Kaplan-Meier method [5]. The

Table 3. Response to chemotherapy

Regimen	1st line				2nd line				Total			
	n	response		RR, %	n	response		RR, %	n	response		RR, %
CBDCA/paclitaxel	5	CR	0	100	1	CR	0	100	6	CR	0	100
		PR	5			PR	1			PR	6	
		SD	0			SD	0			SD	0	
		PD	0			PD	0			PD	0	
CDDP/GEM/VNR	2	CR	0	50	2	CR	0	50	4	CR	0	50
		PR	1			PR	1			PR	2	
		SD	0			SD	1			SD	1	
		PD	1			PD	0			PD	1	
P/E	2	CR	0	50	2	CR	0	50	4	CR	0	50
		PR	1			PR	1			PR	2	
		SD	1			SD	1			SD	2	
		PD	0			PD	0			PD	0	
CPA/ADR based	3	CR	0	0	1	CR	0	100	4	CR	0	25
		PR	0			PR	1			PR	1	
		SD	2			SD	0			SD	2	
		PD	1			PD	0			PD	1	

CBDCA = Carboplatin; CDDP = cisplatin; GEM = gemcitabine; VNR = vinorelbine; P = platinum; E = etoposide; CPA = cyclophosphamide; ADR = doxorubicin; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; RR = response rate.

results were considered to be significant if the calculated p value was <0.05. All data were analyzed using the Abacus Concepts, Survival Tools for StatView software package (Abacus Concepts, Berkeley, Calif., USA).

Results

Treatment Response

The responses to the first-line or second-line chemotherapy for at least 4 patients are summarized in table 3. The patients received the following dosage and schedule of major regimens: carboplatin (CBDCA) area under the treatment and response curve (AUC) = 6 and paclitaxel 200 mg/m^2 on day 1 every 3 weeks, or CBDCA (AUC = 2) and paclitaxel 80 mg/m^2 weekly, cisplatin (CDDP) 40 mg/m^2, gemcitabine (GEM) 800 mg/m^2 and vinorelbine (VNR) 20 mg/m^2 on days 1 and 8 every 4 weeks. Platinum plus etoposide (VP-16; 80–100 mg/m^2 for 3 days) regimens included CDDP (80–100 mg/m^2 on day 1) in 3 patients and CBDCA (AUC = 4 on day 1) in 1 patient every 4 weeks. The cyclophosphamide (CPA)- and doxorubicin (ADR)-based regimens included CPA, ADR, vincristine (VCR) and prednisone (CHOP) in 1 patient, CHOP plus CDDP in 2 and CPA, ADR and VP-16 in 1. The other regimens for 3 or fewer cases were ADR alone, cisplatin plus vindesine, or platinum plus CPT-11. However, there were no responders among patients on these regimens. The median cycle number (range) of CBDCA/paclitaxel-, CDDP/GEM/VNR-, platinum plus VP-16-, or CPA plus ADR-based chemotherapy shown in table 3 as major regimens was 6 (4–7), 4 (1–10), 2 (1–2) or 1 (1–2), respectively. Radiotherapy or chemoradiotherapy was used for the control of the primary site, distant metastases or local recurrence including the localized dissemination nodule. Regimens for concurrent chemoradiotherapy were ADR alone, CPA and ADR-based, or uracil-tegafur (UFT) plus CDDP. The response rate of radiotherapy alone or chemoradiotherapy as initial therapy for the primary site was 17 or 33%, respectively. The total number of treated and measurable lesions and the response rate of radiotherapy or chemoradiotherapy during this study were 22 and 23% or 9 and 33%, respectively.

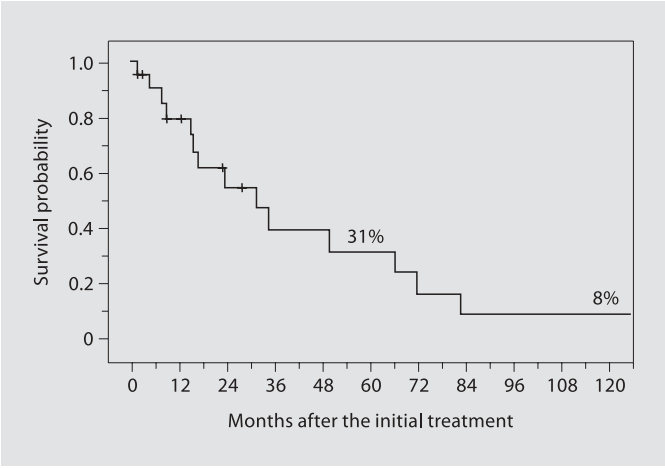

Fig. 1. Overall survival in the patients without a surgical resection for stage I/II disease (median survival time: 32 months).

Survival

Regarding the three main chemotherapy regimens, the median duration of stable disease on CBDCA/paclitaxel, CDDP/GEM/VNR, or platinum plus VP-16 was 11, 8 or 1 months, respectively. The median survival time and the overall survival rate at 5 years for the patients excluding surgical cases with stage I/II disease were 32 months and 31%, respectively (fig. 1).

Discussion

This is a sequel report about the multimodality treatment of TC over a 30-year period, and these findings represent a large single-institutional experience. We previously reported our initial experience of primary TC including two small cell carcinomas, treated with various modalities and followed long-term in our institute [6]. We excluded thymic neuroendocrine tumors in this study. They were classified as typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma, or small cell neuroendocrine carcinoma [2]. Gal et al. [7] showed that thymic neuroendocrine tumors were potentially aggressive tumors that could be morphologically grouped into distinct tumor categories by their analysis of current and previously published cases. The optimal treatment for TC remains to be defined, because the low incidence of this disease has precluded the development of well-designed prospective clinical trials. An initial complete resection is mandatory whenever possible. Radiotherapy plays an important role in treating TC in terms of reducing local recurrence and prolonging the survival time [8]. The role of chemotherapy in treating this malignancy remains controversial, whereas the majority of platinum-based chemotherapy regimens have now been accepted. Recent reports demonstrated a high response rate with combination chemotherapies involving CDDP, ADR, VCR and CPA (ADOC) [9], and CDDP, VCR, ADR and VP-16 (CODE) [10] in Japanese patients with advanced TC. However, these regimens including CPA, ADR and VCR were not effective in this study. A recent study demonstrated the efficacy of doublet chemotherapy consisting of CBDCA and paclitaxel on recurrent thymoma [11] and triplet chemotherapy consisting of CDDP, GEM and VNR on Japanese patients with other thoracic malignancies [12, 13]. Morio et al. [14] recently reported a case which demonstrated induction chemoradiotherapy with CDDP and paclitaxel followed by surgical resection to be useful for advanced TC because no evidence of viable cells was observed in a histopathological examination of the resected specimens and no sign of recurrence was found at 15 months after surgery. Hotta et al. [15] reported that combination chemotherapy consisting of CDDP plus a new agent yields a substantial survival advantage compared with CBDCA plus a new agent in patients with advanced non-small cell lung cancer using a meta-analysis of randomized clinical trials. However, there is no evidence of equivalency between CDDP and CBDCA for this rare malignancy.

Squamous cell carcinoma is the most frequent subtype in Japanese patients with TC (62%) [1]. The prognosis of moderate to poorly differentiated TC depends largely on the microscopic subtype, which is very poor for nonkeratinizing carcinoma (including lymphoproliferative-like tumor), sarcomatoid carcinoma, clear cell carcinoma, and undifferentiated (anaplastic) carcinoma and intermediate for the keratinizing squamous cell carcinoma [16]. Our cases were all nonkeratinizing squamous cell carcinomas. The multimodality approach should be considered to improve the survival of the patients with TC such as those described in this study (median survival time: 36 months, and survival rate at 5 years: 38%).

It is an undeniable fact that the long accrual period of this retrospective study may have resulted in some heterogeneity of the treatment and management of the patients. In the first stage of this study, a CPA/ADR-based chemotherapy regimen was selected, and a regimen including paclitaxel or GEM/VNR was selected in the second stage after the establishment of a new agent. Although the number of cases was too small to draw any

definitive conclusions, we especially feel that doublet chemotherapy consisting of CBDCA and paclitaxel appears to be a promising regimen for TC. The demonstrated antitumor activity is high, thus making this combined chemotherapy worthy of further investigation in a multi-institutional phase II trial.

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