Stage IV Thymic Carcinoma: A Study of 20 Patients

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ABSTRACT: *Background*: This study was performed to investigate the clinical factors, tumor characteristics, treatment approach, and prognosis of patients with Stage IV thymic carcinoma (WHO type C). *Methods*: The records of 20 patients with histologically confirmed thymic carcinoma treated between 1988 and 2002 at the Division of Oncology at Taipei Veterans General Hospital were reviewed. *Results*: Therapy consisted of surgical debulking, adjuvant radiotherapy, and chemotherapy in six patients (30%), surgical debulking with adjuvant chemotherapy in two patients (10%), surgical debulking with adjuvant radiotherapy in one patient (5%), radiotherapy with adjuvant chemotherapy in eight patients (40%), and chemotherapy alone in three patients (15%). After a median follow-up of 22 months (range, 5-72 months), three patients (15%) were alive. Eighteen patients (90%) experienced disease recurrence after a median of 9 months (range, 2-41 months); 12 (66%) of these patients initially had stage IVa disease, and 6 (33%) had stage IV b disease. Five patients had an undifferentiated type of histology. The median time to progression was 5 months. However, none of these patients was able to receive salvage therapy due to their poor performance status. For those patients with a lymphoepithelioma-like histology, the median survival was 36 months; there was tumor recurrence in five patients and they all received salvage chemotherapy. The median survival time for these five patients was 51 months. For patients with squamous cell type, the median time to progression was 10 months. Five patients received salvage chemotherapy and the median survival was 28 months. There was a significant difference ($P < 0.0001$) in the median survival between those who received chemotherapy (18 months) after tumor relapse and those who did not (1 month). *Conclusions*: Our results indicate that multidisciplinary treatment, including surgery, radiotherapy, and chemotherapy, is beneficial in treating primary thymic carcinoma. Chemotherapy plays an important role in both primary and relapsed stage IV thymic carcinoma in terms of prolonging the disease-free survival and median survival of patients with lymphoepithelioma-like or squamous cell histology types. For patients with an undifferentiated histology, multidisciplinary treatment or chemotherapy might not be helpful in either primary or relapsed stage IV thymic carcinoma. **KEY INDEXING TERMS:** Thymic carcinoma; Prognosis; Recurrence. **[Am J Med Sci 2005;330(4):172–175.]**

Thymic carcinoma is a rare neoplasm with distinct pathologic and clinical characteristics. The tumors account for between 5% and 36% of all thymic neoplasms.[1,2] They are aggressive and frequently metastasize and are associated with short patient survival time.[3] However, information about treatment modalities and long-term prognosis in stage IV thymic carcinoma (WHO type C)[4] is limited, and no information is available regarding the treatment modalities for relapsed patients.

In this study, we reviewed the records of 20 patients with advanced thymic carcinoma between 1988 and 2002 and evaluated the treatment modalities and the outcomes.

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Patients and Methods

A review of medical records identified 20 patients with advanced thymic carcinoma at Taipei Veterans General Hospital between 1988 and 2002. The records, histologic data, treatment, and follow-up information of each patient were analyzed.

The histologic specimens in each of these cases were obtained using needle biopsy specimens. Formalin-fixed and paraffin-embedded tissues were reviewed by at least two peer pathologists to confirm the diagnosis and to determine the histologic subtypes, as proposed by Levine et al.[5] The invasiveness of each tumor was evaluated according to the clinical staging procedures of Masaoka and associates[6]: stage I, microscopically encapsulated; stage II, microscopic invasion into the capsule; stage III, invasion into the neighboring organs, such as the pericardium, great vessels, or lung; stage IVa, pleural or pericardial dissemination; stage IVb, lymphogenous or hematogenous metastases. Pretreatment evaluation of the tumor was done by physical examination, chest radiography, computed tomography of chest, abdominal sonogra-

Table 1. Treatment Modalities and Clinical Outcome of 20 Patients with Stage IV Thymic Carcinoma

No.	Sex	Age	Histology	Stage	Treatment	Outcome	Months to Progression	Localization	Salvage Tx	Follow-up
1	F	45	UD	IVa (pc)	S,R,C	SD	9	Neck lymph nodes	–	13
2	F	67	UD	IVa (pl)	R,C	PR	10	Lung, liver	–	13
3	F	66	UD	IVa (pl)	R,C	SD	3	Brain, liver	–	6
4	F	50	UD	IVb (bone)	R,C	PR	5	Lung	–	5
5	M	74	UD	IVb (liver)	R,C	PR	2	Lung	–	3
6	F	31	LE	IVa (pl)	R,C	PR	27	Lung	C	74
7	F	41	LE	IVa (pl)	S,C	CR	–	–	–	44+
8	F	22	LE	IVa (pl)	S,C	CR	–	–	–	23+
9	M	55	LE	IVa (pc)	S,R,C	SD	41	Bone, liver	C	51
10	M	76	LE	IVa (pc)	R,C	PR	10	Mediastinum	C,R	28+
11	F	24	LE	IVb (lung)	S,R,C	PR	27	Neck lymph nodes, skin	C	58
12	M	37	LE	IVb (lung)	S,R,C	PR	9	Bone	C	16
13	M	63	LE	IVb (liver)	S,R	PR	3	Lung	C	22
14	F	39	SCC	IVa (pc)	R,C	SD	7	Mediastinum	C	30
15	F	50	SCC	IVa (pl)	R,C	PR	10	Lung, liver	C	10
16	M	70	SCC	IVa (pl, pc)	S,R,C	SD	36	Retroperitoneum	C	72
17	M	65	SCC	IVa (pl, pc)	R,C	PR	16	Lung	C	28
18	M	48	SCC	IVa (pc)	C	PR	28	Lung	–	28
19	M	51	SCC	IVa (pc)	C	PR	7	Lung	–	7
20	M	71	SCC	IVb (bone)	S,R,C	PR	4	Lung, brain	C	16

C, chemotherapy; CR, complete remission; LE, lymphoepithelioma-like; pc, pericardium; pl, pleura; PR, partial remission; R, radiotherapy; S, surgery; SCC, squamous cell carcinoma; SD, stable disease; UD, undifferentiated.

phy, and bone scans. We analyzed the diagnosis and localization at the initial presentation, extent of staging, treatment, response to treatment, duration of response, recurrence, time to recurrence, salvage treatment, and survival. A partial remission (PR) was defined as a more than 50% decrease in the size of any lesion. Stable disease (SD) was defined as a less than 50% regression of measurable lesions without new lesions. An increase of measurable lesions or the appearance of new lesions was defined as progressive disease (PD). The post-treatment evaluation included a physical examination, chest radiography, and computed tomography. Those patients with CR and PR were rated as nonresponders. Overall survival and recurrence-free survival rates were estimated using the Kaplan-Meier product-limited method.[7] Statistical comparisons between groups were performed by univariate analysis (SPSS version 10.0). Data were analyzed as of January 2003.

Results

Twenty patients (10 males and 10 females) with advanced thymic carcinoma were identified and included in this retrospective evaluation (Table 1). The median age of the patients was 50 years (range, 22-76 years). The extent of thymic carcinoma at the diagnosis was localized as follows: pericardium (n = 6), pleura (n = 6), pleura and pericardium (n = 2), bone (n = 2), lung (n = 2) and liver (n = 2).

At diagnosis, 14 patients presented with stage IVa (70%) disease and 6 patients with stage IVb (30%) disease. Histologic verification by means of biopsy had been performed for all 20 patients included in the analysis. Histologically, there were five patients with undifferentiated cell type (UD), eight patients with the lymphoepithelioma-like type (LE), and seven patients with the squamous cell type (SCC) carcinoma.

One of the 20 patients (5%) had evidence of autoimmune disease (Sjögren syndrome). All patients received treatment of surgical debulking, radiotherapy, chemotherapy, or a combination of treatment modalities.

Therapy consisted of surgical debulking, adjuvant radiotherapy and chemotherapy in six patients (30%), surgical debulking with adjuvant chemotherapy in two patients (10%), surgical debulking with adjuvant radiotherapy in one patient (5%), radiotherapy with adjuvant chemotherapy in eight patients (40%), and chemotherapy alone in three patients (15%). For patients receiving radiotherapy, the radiation dose ranged from 40 cGy to 50 cGy in fractions. Primary chemotherapy consisted of PAC (cisplatin, doxorubicin, and cyclophosphamide) for four patients. In addition, six patients received ADOC (cisplatin, doxorubicin, vincristine, and cyclophosphamide), four patients received CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisolone), four patients received cisplatin and etoposide, and two patients received gemcitabine and cisplatin. Chemotherapy for tumor relapse consisted of cisplatin-based regimens.

Of the 20 patients, 2 (10%) achieved a CR after initial treatment, 13 (65%) achieved a PR, and 5 (25%) a SD. Among the stage IVa patients, 2 (14%) of 14 obtained a CR, 7 (50%) a PR, and 5 (36%) patients had a SD. All patients with stage IVb disease obtained a PR.

After a median follow-up of 22 months (range, 5-72 months), information on survival status was obtained for all patients. Three patients (15%) were still alive at this point.

Eighteen patients (90%) experienced disease recurrence after a median of 9 months (range, 2-41 months). Twelve (66%) of these patients initially had stage IVa disease and six (33%) had stage IVb disease. The pattern of disease recurrence was local in two patients (11%); the others presented with disseminated disease (Table 1).

Among the 18 patients with disease recurrence, initial treatment consisted of chemotherapy only in 10 (55%) patients and combined chemotherapy and radiotherapy in 1 (5%). All disease recurrence was documented histologically as thymic carcinoma.

Discussion

Thymic carcinoma is a rare disease with a poor prognosis.[1] Although data defining the clinical features, pathology, and role of multimodality treatment in thymic carcinoma have been accumulating in the last decade, the treatment for relapsed thymic carcinoma is still evolving.

Several studies have shown that surgery and radiation therapy are the mainstay of the treatment of thymic carcinoma; most of these tumors were locally invasive or metastatic at the diagnosis and the complete resection rates were low.[8] Cisplatin-based chemotherapy has also proved to be effective in the treatment of thymic carcinomas and for those patients with unresectable tumors.[1,9,10] Multimodal treatment, especially complete resection and postoperative radiotherapy with or without chemotherapy, have been suggested to be a curative therapy for thymic carcinoma.[11] Factors such as grade, staging, and resectability of the tumor were also documented to have an impact on the effectiveness of either surgery or chemo/radiotherapies in the treatment of thymic carcinoma.[12] However, for those patients with unresectable stage IV thymic carcinoma, no information regarding the treatment approach is available.

We reviewed 20 cases of stage IV thymic carcinoma in the current study. Interestingly, the patients could be grouped into either a low-risk group (SCC) or a high-risk group (LE and UD) as suggested by Suster et al[1] Tumors in the high-risk group were characterized by a relatively high incidence of local recurrence and distant metastases and thus carried an extremely poor prognosis as compared with those in the low-risk group.

In our study, five patients had an undifferentiated type of histology. The primary treatment approach consisted of radiotherapy and chemotherapy. Only one patient underwent a partial resection in addition to the radiotherapy and chemotherapy. The median time to progression was 5 months. However, none of these patients was able to receive salvage therapy owing to their poor performance status. The median overall survival for these patients was 6 months.

Conversely, for those patients with LE histology, the median survival was 36 months; six of the eight patients underwent an incomplete resection of the tumor before they received either chemotherapy or radiotherapy. Two patients underwent an incomplete resection, then chemotherapy brought about a complete response; the patients were still alive at the time of this study. The median time to progression in the other five patients with tumor recurrence was 18 months, and they all received further salvage treatment with either chemotherapy or radiotherapy and chemotherapy in combination. The median survival time for these five patients was 51 months.

Two patients with SCC-type thymic carcinoma underwent an incomplete surgical resection followed by radiotherapy and chemotherapy. Three patients received radiotherapy and chemotherapy, and two received chemotherapy only. The median time to progression was 10 months. Two patients were not able to undergo salvage therapy owing to the poor performance status. Five patients received the salvage chemotherapy and the median survival was 28 months. None of the patients with the SCC-type of thymic carcinoma was alive at the time of this study. In addition, there was also a significant difference ($P < 0.0001$) in the median survivals between those who were treated with chemotherapy (18 months) after tumor relapse and those who were not (1 month).

The histologic classification of thymic carcinoma has been important because of its prognostic significance,[1,13] with the SCC-type thymic carcinoma having the most favorable prognosis. Several reports have indicated the better median survivals in the

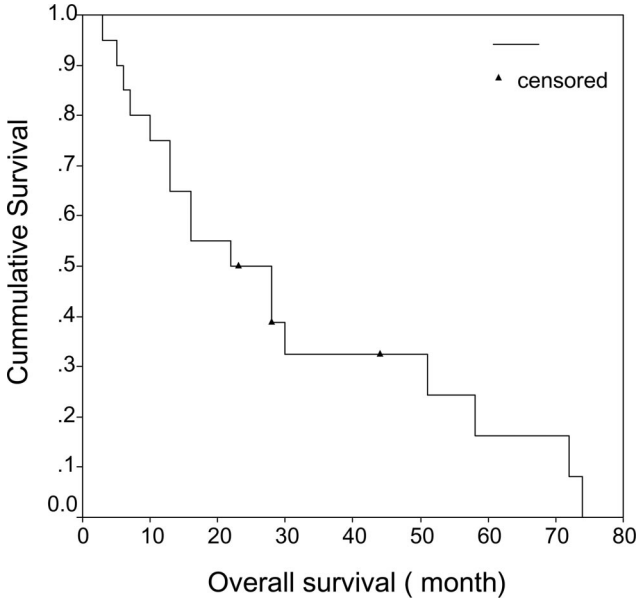

Figure 1. Overall survival for 20 patients with stage IV thymic carcinoma.

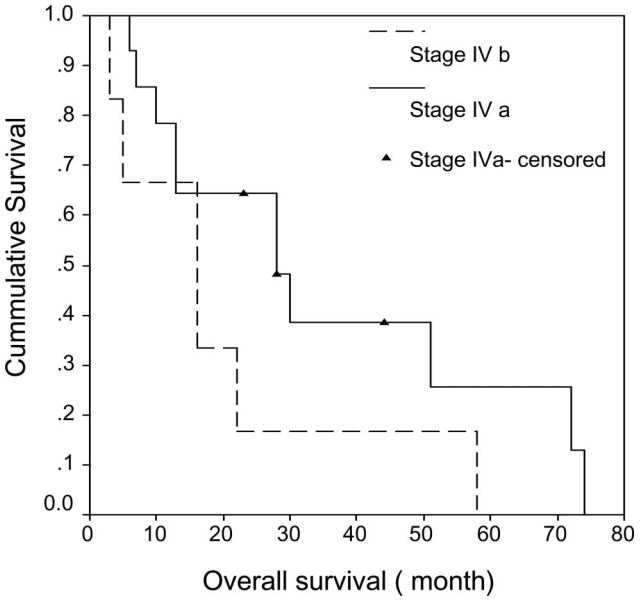

Figure 2. Overall survival for 20 patients based on the stage classification.

high-risk group of thymic carcinoma patients compared with the low-risk group with survivals of 25.4 to 49 months and 11.3 to 18 months, respectively. In our study, however, patients with the UD-type responded poorly to the treatment modalities and had a short survival time. Conversely, for patients with the LE histology, longer disease-free survivals were achieved. The salvage chemotherapy achieved better median survivals than those reported. This might be due to the heterogeneous groups of patients included in other studies. Our study also showed comparable median survivals for patients in the low-risk group (SCC) as previously reported.[14]

Conclusions

Our results suggested that chemotherapy plays an important role in both primary and relapsed stage IV thymic carcinoma in terms of prolonging the disease-free survival times and the median survivals of patients with LE or SCC histologic types. For patients with the UD histology, multifaceted treatment or chemotherapy might not be helpful in either primary or relapsed stage IV thymic carcinoma (Figures 1 and 2).

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