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Chemotherapy of Thymic Carcinoma: Analysis of Seven Cases and Review of the Literature

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Background: Thymic carcinoma has a dismal prognosis compared with thymoma, because most of such tumors have locoregional invasion when diagnosed. Thus the important step in the management of thymic carcinoma is the introduction of systemic chemotherapy. However, as thymic carcinoma is a rare neoplasm, treatment with chemotherapy has not been studied systematically.

Methods: We analyzed seven cases of primary thymic carcinoma, treated with various chemotherapy regimens in our hospital from 1990 to 1999, and carried out a literature review of case reports of thymic carcinoma successfully treated with chemotherapy.

Results: All four cases who received modified ADOC therapy obtained partial responses. Other chemotherapeutic regimens (CHOP-E, PVB) were not effective.

Conclusion: Based on the results of this study and the literature review, we feel that a positive response is obtainable with chemotherapy for thymic carcinoma. Modified ADOC therapy showed consistent efficacy in thymic carcinoma in this study.

Key words: thymic carcinoma – chemotherapy – modified ADOC therapy

INTRODUCTION

Both thymic carcinomas and thymomas are neoplasms of the thymic epithelial cells, but thymic carcinomas are obviously histologically malignant and generally are not associated with any parathymic syndromes (1). Thymic carcinoma has a dismal prognosis compared with thymoma, because most such tumors have locoregional invasion at the time of diagnosis. Thus an important step in the management of thymic carcinoma is the introduction of systemic chemotherapy. However, because thymic carcinoma is a rare neoplasm, treatment with chemotherapy has not been studied systematically. Here, we present seven cases of primary thymic carcinoma, treated with various chemotherapy regimens, and include a literature review of case reports of thymic carcinoma which obtained partial or complete response with chemotherapy.

MATERIALS AND METHODS

From 1990 to 1999, there were 13 cases of primary thymic carcinoma (12 men and one woman; median age, 50 years; range, 33–71 years) at the Showa University Fujigaoka Hospital. Eight patients were treated with chemotherapy and the efficacy of this chemotherapy could be evaluated. One patient was a previously reported case, who also had acute monocyte leukemia (AMoL) and obtained partial remission after initial treatment with DCMP therapy: daunorubicin, cytosine arabinoside, 6MP-ribose and predonisolone, followed by five courses of consolidation chemotherapy against AmoL (2). We considered seven other cases in this study (Table 1). The diagnostic criteria of primary thymic carcinoma were based on the existence of an anterior mediastinal tumor at the thymic region showing histological features of malignancy, as proposed by Shimosato and Mukai (3). Formalin-fixed and paraffin-embedded tissues were used for the histopathological and immunohistochemical examinations and frozen sections were used for the analysis of lymphocyte subsets in the tumor by flow cytometry in some cases. Clinical stage was assessed according to criteria proposed by Masaoka et al. (4): stage I, microscopically encapsulated; stage II, microscopic invasion into capsule; stage III, invasion into the neighboring organs, (i.e. pericardium, great vessels or lung); stage IVa, pleural or pericardial dissemination; stage IVb, lymphogenous or hematogenous metastases. All seven patients who received chemotherapy were evaluated for efficacy by chest computed tomography (CT) after one to three cycles of treatment. Partial remission (PR) was defined as a >50% decrease in the size of the main measurable lesions without an increase in the size of any lesions or the appearance of new lesions lasting at least 4 weeks. No change (NC) was

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Table 1. Clinical findings in seven cases of thymic carcinoma

Case	Age (years)/ gender	Pathology	Stage	Timing of chemotherapy	Regimen of chemotherapy	No. of courses	Response	Response duration (months)	Outcome (months)
1	46/M	p/d SCC	IVa	Inoperable	PVB	2	NC		13, dead
2	67/M	Anaplastic carcinoma	IVb	Recurrence	CHOP-E	2	NC		17, dead
3	61/M	Anaplastic carcinoma	IVa	Inoperable	PVB	2	NC		18, dead
4	47/M	Anaplastic carcinoma	III	Inoperable	m-ADOC	2	PR	15	34, alive
5	64/M	Anaplastic carcinoma	IVb	Inoperable	m-ADOC	3	PR	10	18, dead
6	32/M	m/d SCC	IVb	Inoperable	m-ADOC	5	PR	7	16, alive
7	50/M	m/d SCC	IVb	Inoperable	m-ADOC	3	PR		3, alive

SCC, squamous cell carcinoma; PR, partial response; NC, no change; PVB, cisplatin, vinblastine, bleomycin; CHOP-E, vincristine, cyclophosphamide, adriamycin, prednisolone, etoposide; m-ADOC (modified ADOC), adriamycin, nedaplatin, cyclophosphamide, vincristine; p/d, poorly differentiated; m/d, moderately differentiated.

defined as <50% regression of measurable lesions without new lesions for at least 4 weeks. An increase of measurable lesions or the appearance of new lesions was considered as progressive disease (PD).

Modified ADOC therapy [50 mg/m^2 of nedaplatin (CDGP) on day 1, 40 mg/m^2 of doxorubicin on day 1, 0.6 mg/m^2 of vincristine on day 3, 700 mg/m^2 of cyclophosphamide on day 4) was performed as follows. Nedaplatin was given i.v. in 500 ml of normal saline over 3 h. Following administration of nedaplatin, doxorubicin was given i.v. in 100 ml of normal saline over 30 min on day 1. Vincristine was given i.v. in 100 ml of normal saline over 30 min on day 3. Cyclophosphamide was given i.v. in 100 ml of normal saline over 30 min on day 4. To control drug-induced emesis, azasetrone (10 mg) was given i.v. in 100 ml of normal saline from day 1 to day 4. Patients did not receive prophylactic G-CSF. This modified ADOC therapy was performed for at least two courses at 4-week intervals. All patients gave verbal informed consent.

RESULTS

The clinical stages were stage III in one case, stage IVa in two cases and stage IVb in four cases. Multiple pulmonary metastases were seen in cases 6 and 7 and cervical lymph nodes and femur metastasis in cases 2 and 7, respectively. The histopathological types of the tumors were squamous cell carcinoma in three cases and anaplastic carcinoma in four cases. All patients except cases 4 and 5 received systemic chemotherapy against the main tumor, pulmonary and bone metastatic or pleural disseminated lesions. Cases 4 and 5 were initially treated with intra-arterial infusion chemotherapy via the internal thoracic artery. The timing of the chemotherapy was when judged inoperable in six cases and at recurrence after operation in one case. Cases 1 and 3 had two courses of chemotherapy with PVB therapy: 100 mg/m^2 of cisplatin on day 1, 0.15 mg/kg of vinblastine on days 1 and 2 and 15 IU/m^2 of bleomycin on days 2, 8, 15 and 21. Case 3 received CHOP-E therapy. These three cases did not achieve tumor regression. They were also treated with radiation therapy of 4000 cGy to the primary tumor, but tumor regression was not obtained and they died 13–18 months after the first chemotherapy. The recent cases 4, 5, 6 and 7 received a regimen of modified ADOC therapy in the method as mentioned above. These four cases obtained PR after one to three courses of the modified ADOC therapy.

Toxicity was graded according to the World Health Organization (WHO) (5). The modified ADOC regimen was well tolerated. Grade one or two myelosuppression occurred in all four patients who received the modified ADOC therapy, but three of the four patients recovered without G-CSF. Grades one or two nausea and anorexia occurred in three patients. Renal, liver and cardiac functions were not affected by the modified ADOC therapy. Red skin rash in the anterior chest occurred in case 4, who received the modified ADOC therapy with intra-arterial infusion via the internal thoracic artery.

DISCUSSION

Thymic carcinoma is defined as a thymic epithelial tumor with a high degree of histological anaplasia, obvious cell atypia and increased proliferative activity, which closely resembles carcinoma seen in other organs and is unassociated with immature T cells (3). Compared with thymoma, thymic carcinoma has a more invasive tendency and sometimes metastasizes to mediastinal or cervical lymph nodes, bone, lung and liver.

The major cause of initial treatment failure in patients with invasive thymoma is local, intrathoracic recurrence. On the other hand, distant metastasis remains the major determinant of survival in thymic cancer. Based on the above factors, chemotherapy seems indispensable as therapy for thymic carcinomas.

Because thymic carcinoma is a rare neoplasm, the role of chemotherapy in thymic carcinoma is unclear at the moment. To date, the largest series of primary thymic carcinomas reported was that described by Suster and Rosai, which comprised 60 patients (6). They stated that no obvious beneficial effects from the administration of chemotherapy were apparent in their series. Recently, however, a few reports have cited the efficacy of chemotherapy in treating thymic carcinoma (Tables 2 and 3) (7–19). The successful applications of chemotherapy

Table 2. Combination chemotherapy in thymic carcinoma*

Regimen	No. of patients	Response	Reference
PE + epirubicin: cisplatin, etoposide, epirubicin	3	3/3 (3 PR)	Macchiarini et al. (11)
PE + bleomycin: cisplatin, etoposide, bleomycin	3	3/3 (2 CR, 1 PR)	Weide et al. (14)
PAC + vincristine: cisplatin, adriamycin, cyclophosphamide, vincristine	2	0/2	Yano et al. (15)
PAC + etoposide: cisplatin, adriamycin, cyclophosphamide, etoposide	7	4/7 (4 PR)	Oshita et al. (17)
VAC: vincristine, adriamycin, cyclophosphamide	2	2/2 (2 PR)	Yano et al. (15)

PR, partial response; CR, complete response. *Excluding the regimen of single case reports.

Table 3. Effective cases of chemotherapy for thymic carcinomas

Series		Age (years)/ gender	Histology type	Primary treatment	Chemotherapy regimen	Response to CT	Outcome (after diagnosis)	Ref.
Leyvraz et al.	1985	19/M	LE	CT, RT	CDDP, Bleo, ADM, prednisone	CR	Dead 11 mo, liver metastasis	7
Thomas and Manivel	1987	59/M	PD	RT, CT	CDDP, VCR, prednisone	PR	Unknown, liver metastasis	8
Dimery et al.	1988	30/F	LE	CT, RT	CDDP, ADM, CPA, prednisone	CR	Alive, 24 mo	9
Carlson et al.	1990	21/M	PD	CT, Re	CDDP, Bleo, VBL	CR	Alive 64 mo, NED	10
Macchiarini et al.	1991	51/M	LE	CT, cRe, RT	CDDP, etoposide, epirubicin	PR	Unknown	11
		26/M	LE	CT, cRe, RT	CDDP, etoposide, epirubicin	PR	Alive 33 mo, NED	
		32/M	SCC	CT, cRe, RT	CDDP, etoposide, epirubicin	PR	Alive 30 mo, NED	
Tweedy et al.	1992	55/M	?	CT, RT	Carboplatin, etoposide	CR	Alive 8 mo, NED	12
Yonekura et al.	1992	34/M	?	RT, CT	VCR, CPA, ADM, prednisolone	PR	Dead 15 mo, leukemia	13
Weide et al.	1993	44/M	SC + SCC	pRe, CT	CDDP, Bleo, etoposide	PR	Unknown	14
		55/F	UD (LC)	OP, CT, RT	CDDP, VBL, ifosamide	CR	Dead 36 mo, lung metastasis	
		35/M	PD SCC	RT, CT	CDDP, ADM, CPA	CR	Unknown	
Yano et al.	1993	36/F	SCC	RT, CT	CPA, ADM, VCR	PR	Dead 11 yr, skin metastasis	15
		50/M	SCC	pRe, RT, CT	CPA, ADM, VCR	PR	Alive 30 mo, liver metastasis	16
Hsu et al.	1994	?/F	SCC	CT, cRe	CPA, ADM, VCR, CPA	PR	Dead 23 mo (after operation)	
Oshita et al.	1995	?/?	PD	CT, ?	CDDP, ADM, CPA, etoposide	PR	Unknown	17
		?/?	PD	CT, ?	CDDP, ADM, CPA, etoposide	PR	Unknown	
		?/?	PD	CT, ?	CDDP, ADM, CPA, etoposide	PR	Unknown	
Yanagawa et al.	1995	48/M	UD	CT, RT	CDDP, ADM, VCR, etoposide	PR	Dead 18 mo (after CT)	18
Niehues et al.	1996	14/M	LE	Re, CT, RT	CDDP, etoposide, ifosamide	CR	Alive 12 yr	19

CDDP, cisplatin; Bleo, bleomycin; VCR, vincristine; CPA, cyclophosphamide; ADM, doxorubicin; LE, lymphoepithelioma-like; PD, poorly differentiated; UD, undifferentiated; SCC, squamous cell; SC, small cell; LC, large cell; CT, chemotherapy; TR, radiation therapy; pRe, partial resection; cRe, complete resection; CR, complete response; PR, partial response; NED, no evidence of disease; mo, months; yr, years.

for thymic carcinoma have almost all used a cisplatin-containing regimen, originally used to treat advanced thymoma or germ cell tumor. We determined the regimen of chemotherapy to be used in the present study by referring to those successful cases.

Carlson et al. (10) described the first successful chemotherapy treatment case of metastatic undifferentiated thymic carcinoma. They used combination chemotherapy with cisplatin, vinblastine and bleomycin (PVB), which is the standard regimen for germ cell tumors, and obtained a pathological complete response. We used this regimen for the two early patients, but these patients showed no response. On the other hand, we obtained a partial response in the four more recent cases, who received modified ADOC therapy. Chemotherapy with the ADOC regimen was reported by Fornasiero et al. in 1991 (20). This regimen achieved a high response rate for invasive thymoma and recently there were some successful cases using ADOC or modified ADOC chemotherapy for thymic carcinoma. We used nedaplatin [*cis*-diammine(glycolato)platinum] (21) in place of cisplatin in original ADOC therapy owing to the slight disturbance of renal function seen with the use of cisplatin.

We treated two early cases (cases 4 and 5) with modified ADOC therapy by intra-arterial infusion through the internal thoracic artery. Case 4 was stage III thymic carcinoma that was suspicious of anterior chest wall invasion on chest CT, so we first applied intra-arterial infusion chemotherapy. This case has been reported previously (22). Because our cases and other reported cases of thymic carcinoma treated with intra-arterial infusion chemotherapy are small in number, the efficacy of intra-arterial infusion chemotherapy is unclear. There were no apparent differences in tumor regression between intra-arterial and intravenous infusion in the four cases who received modified ADOC therapy in this study.

A variety of histopathological subtypes of thymic carcinoma have been reported, so it is assumed that the responses to chemotherapy of thymic carcinoma differ among histopathological subtypes. However, the effective cases of chemotherapy for thymic carcinoma included both squamous cell carcinoma and poorly or undifferentiated carcinoma almost equally. In the present study, three were squamous cell carcinomas and four were anaplastic cell carcinomas. Modified ADOC therapy was effective for squamous cell and aplastic cell thymic carcinoma. On the other hand, PVB therapy was not effective for either of the above subtypes of thymic carcinoma. Thus we did not find differences in chemotherapeutic response between squamous cell carcinoma and anaplastic cell or undifferentiated carcinoma in this study or in the review of the literature.

We speculated as to which drug was the key component in the regimen used in our cases. As mentioned above, the successful applications of chemotherapy for thymic carcinoma almost all used a platinum-containing regimen, but PVB chemotherapy in this study was not effective for thymic carcinoma. The PVB regimen consists of a higher dosage of platinum drug than the ADOC regimen. Hence we think that it is doubtful that a platinum drug alone is the first key drug. On the other hand, regimens including anthracycline (doxorubicin, epirubicin) were effective in many cases. It is noted that Yano et al. (15) reported two successful cases using a regimen without a platinum drug (CPA, ADM, VCR) for thymic squamous cell carcinoma. From these facts, it is concluded that anthracycline is necessary in the regimen for thymic carcinoma whether or not a platinum drug is included.

Although we obtained partial responses in four cases with thymic carcinoma, in three of these four cases regrowth of the main tumor or metastatic lesions occurred at an interval of 7–15 months. Hence we expect the establishment of a more effective regimen for thymic carcinoma.

CONCLUSION

Although the number of cases in this study is small, the findings following chemotherapy appear to indicate a positive response. Modified ADOC therapy showed consistent efficacy in thymic carcinoma in this study.

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