Systemic Treatment of Malignant Thymoma
A Decade Experience at a Single Institution

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Objectives: Thymic malignancies are rare tumors on the superior anterior mediastinum. Treatment of advanced stages includes chemotherapy. The objective of this analysis was to review the treatment of this disease in the past decade.

Methods: This is a retrospective analysis of the results obtained in a total of 29 patients with advanced malignant thymomas who underwent systemic chemotherapy in the past 10 years at our institution. Sixteen received neoadjuvant chemotherapy in the attempt to shrink the tumor and then perform a radical operation. The others received chemotherapy as palliation. Platinum based chemotherapy was mainly used.

Results: The response rate to first-line chemotherapy was 50% in the neoadjuvant setting and 31% in the advanced setting. A better survival was observed in patients who underwent chemotherapy as part of their combined modality treatment, in patients with thymomas, and in patients without visceral metastases. Some patients responded to targeted therapies at relapse.

Conclusions: A better understanding of the biology of this rare tumor may allow in the future the development of better therapies for the more aggressive tumor types (WHO type C), which appear to be increasing in frequency.

Key Words: thymoma, chemotherapy, targeted therapy

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Thymomas are the most common tumors arising from the thymus.[1] Although thymomas are histologically benign tumors, thymomas are potentially invasive through the capsule and can infitrate the surrounding organs and great vessels. Furthermore, thymomas, albeit rarely, can metastasize to distant organs. Although the classification of thymomas remains a source of debate, there is general agreement that the epithelial cells represent the tumor cells and the lymphocytic cells are considered benign infiltrating cells.[2] In 1999, the World Health Organization (WHO) panel achieved an agreement to the classification system based on the morphology of epithelial cells as well as the lymphocytic to epithelial cell ratio.[3] The WHO classification is depicted in Table 1. In type A tumors the thymic epithelial cells and their nuclei have a spindle and/or oval shape, resembling *A*trophic thymic tissue. In type B tumors these cells have a more dendritic or plump appearance, creating a resemblance with *B*ioactive thymic tissue. Tumors that combine these 2 morphologies are designated type AB. Type B tumors are still subdivided, based on the proportional increase of the epithelial component and the atypia of the neoplastic cells. All thymic carcinomas are categorized as type C (*c*arcinoma). Several other classifications have been reported, that are of less general use. Basically there appears to be a continuum of histologic changes from pure thymoma (histologically benign tumor) to thymic carcinoma (histologically malignant tumor, poorly differentiated).[3]

Surgery is the cornerstone of therapy for patients presenting with a localized tumor.[4] However, often patients with thymomas present with large mediastinal masses and few symptoms, and it may be hard to assess operability by preoperative investigations. As these tumors appear to be sensitive to chemotherapy, recently the tendency is to deliver preoperative chemotherapy in the attempt to reduce the morbidity of the operation or the fields of radiotherapy.[5] Moreover, operation, even when not radical and with debulking purposes only, has been shown to be an important therapeutic measure, especially in thymomas, which have a slow growth, and where cytoreduction of large masses allows prolongation of survival.[6]

Thymomas are exceptionally rare tumors (overall incidence 0.15 per 100.000 person-year),[7] and the largest series report on surgical results. Relatively small series report studies of multimodality treatment or systemic therapy. No randomized study was ever performed with any treatment modality in this disease.

Interestingly, in reviewing the literature, it appears that in recent years more patients with thymic carcinomas are included in clinical trial series.[8,9] This may be a reflection of the changing histologic classification or it may be a true change in malignant phenotype of these tumors. Alternatively, probably several of the large mediastinal masses where the histologic classification was difficult were classified as metastatic undifferentiated carcinomas of unknown origin in the past, or a lung origin was suggested. Presently, with the introduction of more sophisticated staging tech-

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TABLE 1. World Health Organization Pathological Classification of Thymoma[3]

Type	Histologic Description
A	Medullary thymoma
AB	Mixed thymoma
B1	Predominantly cortical thymoma
B2	Cortical thymoma
B3	Well-differentiated thymic carcinoma
C	Thymic carcinoma

niques, such as FDG-PET scanning, several of the mediastinally localized undifferentiated carcinomas can now be reclassified as of thymic origin (WHO type C), in absence of a primary tumor elsewhere. FDG-PET scanning is positive in tumors that are highly aggressive and less so in better differentiated tumors or benign lesions.[10]

Thymoma has been known as a relatively radiosensitive tumor and adjuvant radiotherapy improves local control and survival. The role of radiotherapy after a radical operation of an early stage thymoma is, however, controversial. Systemic chemotherapy is capable of producing durable remissions in over 50% of patients with unresectable or metastatic disease. Several small chemotherapy series have been reported and the largest experience was reported with cisplatin based regimens. A few studies have reported on the use of neoadjuvant chemotherapy to improve tumor resectability.[11] This treatment modality has become a standard in several centers when tumors appear not to be easily resectable on the base of preoperative assessments. A number of patients will relapse after first-line therapy, but very few data are presently available on the treatment of refractory or relapsed disease.

In this study we report our experience in the treatment of patients with thymoma and thymic carcinoma with systemic therapy. In recent years, the introduction of targeted agents in the therapy for several hematological malignancies and solid tumors may also have a bearing in the therapy for this rare tumor. More biologic studies are warranted to discover potential targets amenable to targeted therapies.

PATIENTS AND METHODS

Patients

A retrospective review of medical records identified 29 patients who were treated between 1995 and August 2005 for a diagnosis of malignant thymoma at the VU University Medical Center in Amsterdam. In all these cases chemotherapy was given either as palliation or as neoadjuvant therapy in the setup of a combined modality approach. Patients were informed about the prognosis and the treatment, according to national and local policies. Histology was centrally reviewed by one of us (P.V.) and classified according to the WHO classification (Table 1).[3] In cases of thymic carcinoma (WHO type C) the diagnosis was sometimes by exclusion of another primary tumor outside the mediastinal mass. The use of PET scanning was frequently performed in more recent years as part of the work-up of these tumors. Staging was according to the Masaoka staging system (Table 2).[2]

Treatment

Surgery was performed using a median sternotomy approach in all cases, but in some cases a lateral thoracotomy was also added to adequately access the pleural and lung metastases.

Radiotherapy was administered as adjuvant up to a dose of 60 Gy in patients who underwent resection of their tumor after neoadjuvant chemotherapy. Radiotherapy was given in 2 cases as initial treatment because of acutely ensued superior vena cava syndrome.

Several chemotherapy regimens were used. Most first-line chemotherapy was platinum based. This series only includes patients who were thought to be either unresectable but potentially resectable after neoadjuvant chemotherapy, or patients with advanced metastatic disease where operation was excluded. Surgery was also attempted in presence of metastases in the pleura and the lung if these were felt to be radically resectable. Patients who were not eligible for local treatment received chemotherapy alone. Treatment-decision making was performed based on stage and extension of disease. Response to chemotherapy was evaluated according to the RECIST criteria.[12] Patients who relapsed after first-line treatment received a number of novel agents.

Statistics

The survival from diagnosis was calculated from the day of diagnosis to the date of death or last known to be alive. The survival from chemotherapy was calculated from the first day of chemotherapy to the date of death or last known to be alive. The survival curves were constructed using the Kaplan-Meyer method and survival curves were compared using the log-rank test. Comparisons between groups were performed using the χ^2 test.

RESULTS

The main patient characteristics are shown in Table 3. The mean age at start of chemotherapy was 50 years, and there was a relatively short interval between diagnosis and

TABLE 2. Masaoka Clinical Staging of Thymoma[36]

Stage	Diagnostic Criteria
I	Macro- and microscopically completely encapsulated (tumor invading into but not through the capsule is included)
II	A. microscopic transcapsular invasion
	B. Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium)
III	Macroscopic invasion into neighboring organs (ie, pericardium, great vessels, or lung)
	A. without invasion of great vessels
	B. with invasion of great vessels
IV	A. Pleural or pericardial dissemination
	B. Lymphogenous or hematogenous metastases

TABLE 3. Patient Characteristics (n = 29)

Characteristics	No. Patients
Age at start of chemotherapy (years)	
Mean	50
Range	25–82
Gender	
Male	16
Female	13
Histology (WHO classification)[3]	
Thymoma	
B1	1
B2	10
B3	6
C	12
Paraneoplastic syndrome	
Myasthenia gravis	5 (1 developed after operation)
Pure red cell aplasia	1 (developed after operation)
Masaoka staging[2] at time of chemotherapy	
IIIA	2
IIIB	4
IVA	7
IVB	16
Metastases	
Yes	21
No	8
Sites of metastases	
Pleura	5
Pleura + lung	4
Pleura + bone	1
Pleura + liver + lymph nodes	1
Pleura + peritoneum	1
Lymph nodes	4
Liver	1
Bone + liver	1
Bone + liver + lymph nodes	1
Lung + bone + liver	1
Trachea	1
Other malignancies	
No	26
Yes	3
Chemotherapy given as	
Neoadjuvant	16
Palliation for advanced disease	13

start of chemotherapy in this group of patients with mainly advanced stages of disease. Between diagnosis and start of chemotherapy there was a mean of 19.5 months (range, 0–187). There was no difference in mean age between the thymic carcinomas (WHO type C) and the thymomas. Paraneoplastic syndromes were diagnosed in 6 patients, being myasthenia gravis in 5 and pure red cell aplasia in 1; none of the syndromes developed in thymic carcinomas. The patient with pure red cell aplasia responded to treatment with prednisone and the aplasia disappeared after 6 months of treatment and did not recur since. Two of these syndromes developed after operation. Other malignancies, all hematological, were reported in 3 cases, 2 before the diagnosis of thymoma and one after treatment of thymoma. One patient was successfully treated with mantle radiotherapy for a stage IA Hodgkin disease 34 years before, and again irradiated for a recurrence in the neck 12 years later. Another patient was successfully treated with combination chemotherapy for a stage III non-Hodgkin lymphoma 13 years earlier. The third patient developed acute T cell leukemia after failure of chemotherapy and while he was on therapy with a phase I agent.

In total 16 patients underwent chemotherapy as neoadjuvant therapy followed by surgery when feasible, or radiotherapy when this was not possible. Several patients received adjuvant radiotherapy after the operation. The remaining 13 patients received chemotherapy as palliation.

FDG-PET scanning was performed in 9 patients (see Tables 4 and 5). It was positive in all 7 patients in whom the scan was performed before treatment; in 2 patients where the scan was negative, it was performed after therapy. In patient 7 the PET scan turned positive when relapse occurred. These results confirm that thymomas are usually positive on FDG-PET imaging.

Neoadjuvant Chemotherapy

Sixteen patients received neoadjuvant chemotherapy (Table 4). Six had stage III disease, 4 stage IVA, and 6 stage IVB on the basis of ipsilateral lung and pleural metastases in 2 cases and mediastinal lymphadenopathy in 4 cases. The neoadjuvant regimen was VIP (etoposide, ifosfamide, cisplatin)[13] chemotherapy in 12 patients. One patient received CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy because she was initially diagnosed as a NHL, and one received carboplatin-gemcitabine because this patient was initially diagnosed as a stage III nonsmall cell lung cancer. Carboplatin-etoposide was used in a 82-year-old women who was not considered able to tolerate VIP chemotherapy, and ADOC (cisplatin, doxorubicin, vincristine, cyclophosphamide)[14] was used in a patient with SVC syndrome, who was thought not to be able to tolerate the prolonged hyper-hydration required for the VIP. ADOC was initially also used in another patient, but because only stabilization was achieved after 2 cycles, chemotherapy was changed into VIP. Usually at least 4 cycles of chemotherapy were given before the local treatment was instituted. The local therapy was operation in 9 patients. One patient with myasthenia gravis died of respiratory insufficiency after the operation. The operation was not thought feasible in the other patients because of insufficient response to chemotherapy and patients received radiotherapy (n = 4). One patient who had received radiotherapy acutely for a superior vena cava syndrome (SVC) was still not operable after a partial remission obtained with 6 cycles of VIP, because of encasement of the great vessels. Five patients who were operated received adjuvant radiotherapy and 2 patients received additional chemotherapy. The response rate to induction chemotherapy was 8 partial responses out of 16 evaluable patients (50%). All 8

TABLE 4. Neoadjuvant Chemotherapy

Patient No.	Histology	Stage	Gender	Age at Chemotherapy	Neoadjuvant Treatment	Response	Local Treatment	Adjuvant Treatment	Time to Progression From Last Therapy (mos)	Further Treatment	Survival (mos)
5	C	IVA	F	25	4 × VIP	PR	Operation (tumor spill)	1 × VIP	3	PG (PD)	15
7	B3	IIIB (SVC)*	F	45	RT (60Gy)-6 × VIP	PR	—	—	6	CT (NC); RT, gefitinib (PD); octreotide+prd (PD); SU14813(NC); capecitabine (NE); bevacizumab (PD)	44+
8	B2	IVB, pleura, lung*	M	32	2 × ADOC 2 × VIP	NC (7%)†	Operation (irradical)	—	—	Died of post-operative complications (MG)	6
9	B3	IIIB*	M	41	5 × VIP	NC (20%)	Operation (radical)	RT60Gy	—	—	NED (46+)
10	C	IIIA	F	37	4 × VIP	PR	Operation (irradical)	2 × VIP RT 36 Gy	—	—	NED (106+)
11	B2	IIIA*	F	45	4 × VIP	PR	Operation (radical)	RT56Gy	—	—	NED (45+)†
12	B2	IVA	F	45	6 × CHOP	PR	Operation (radical)	—	—	Developed pure red cell aplasia	NED (48+)
13	B2	IVB lfn	F	51	4 × VIP	NC (5%)	Operation (irradical)	RT60Gy	18	CT (NC); TG (PD)	37
14	C	IVB lfn*	M	57	4 × VIP	NC (3%)	RT (24 Gy) (PR)	—	11	PG-SU5416 (PD)	18
15	C	IVB lfn	F	77	2 × VIP	PR	RT 60 Gy	—	—	—	31+
16	B2	IVA	M	35	4 × VIP octreotide/ prd	NC (8%)	Operation (irradical)	RT60Gy	—	—	NED (21+)
23	B3	IIIB	F	82	4 × CV	NC (5%)	RT (60 Gy)	—	—	Developed MG	15+
24	B2	IVA*	M	63	5 × VIP	NC (10%)	Operation (irradical)	—	—	—	NED (13+)
26	C	IVB lfn (SVC)	F	44	5 × ADOC	NC (10%)	RT 60 Gy + cisplatin	—	9	CT (NE perforation)	13
27	C	IIIB	M	59	6 × CG	PR	RT (5 Gy × 5)	—	—	Operation (pCR)	NED (27+)
30	B2	IVB pleura, lung	F	54	VIP	PR			—	Neoadjuvant chemotherapy ongoing	2+

*FDG-PET performed.

†In parenthesis, the actual percentage of tumor shrinkage.

lfn, mediastinal lymphadenopathy; SVC, superior vena cava syndrome; RT, radiotherapy; PR, partial response; NC, no change; PD, progressive disease; MG, myasthenia gravis; P, cisplatin; G, gemcitabine; C, carboplatin; T, paclitaxel; prd, prednisone; V, etoposide; VIP, etoposide, ifosfamide, cisplatin; ADOC, doxorubicin, cisplatin, vincristine, cyclophosphamide; NED, no evidence of disease.

TABLE 5. Chemotherapy for Advanced or Recurrent Disease

Patient No.	Histology	Stage at Chemotherapy	Gender	Age at Chemotherapy	First-Line Chemotherapy	Response	Time to Progression (mos)	Further Therapy	Survival (mos)
1	B3	Recurrent after radical operation-RT (46 Gy) IVB pleura, bone	M	56	6 × PV	NC	4	Palliative RT	20
2	B1	Recurrent after irradical operation and 4 adjuvant BEP cycles; IVB pleura, peritoneum	M	57	4 × VIP	NC	16	Ocreotide + prd (PR)	44+
4	B2	Recurrent after radical operation; IVA	F	38	2 × VIP	NE	—	Died of lung insufficiency (MG and infection)	1
6	C	Recurrent after RT (SVC); IVB trachea	M	51	6 × PV	NC	6	—	14
17	B2	IVB pleura, lung*	M	45	2 × PV	PD	—	CAP (NC); octreotide-pdn (PR); SU14813 (NC)	22 (died of acute T cell leukemia)
18	B3	IVB pleural, lung	M	56	6 × CV	NC	7	Ocreotide (PD)	31+
19	C	IVB pleura, liver, lymph nodes	M	42	3 × CAP	NC	5	CT (PD); 5FU/LV (short PR); imatinib (PD)	12
20	B3	Recurrent after radical operation; IVA	M	45	4 × VIP	NC	17	KRN7000 (NC)	35
21	C	IVB liver	M	69	4 × VIP	PR	7	KRN7000 (PD)	15
22	C	IVB liver, bone, lung	F	36	4 × VIP	PR	5	Doxorubicin-V (PD)	17
25	B2	IVA (SVC)	F	56	VEP	PR	18	Radiotherapy; gefitinib (NC); octreotide + prd (NC); CT (NC)	45+
28	C	IVB bone, liver*	M	35	5 × VIP	NC	3	Imatinib (NE intolerance)	8
29	C	IVB bone, liver, lymph nodes	M	64	VIP	PR	—		5

*FDG-PET performed.

SVC, superior vena cava syndrome; RT, radiotherapy; PR, partial response; NC, no change; PD, progressive disease; NE, nonevaluable; P, cisplatin; V, etoposide; C, carboplatin; CAP, cyclophosphamide, doxorubicin, cisplatin; VEP, etoposide, epirubicin, cisplatin; T, paclitaxel; BEP, bleomycin, etoposide, cisplatin; prd, prednisone; VIP, etoposide, ifosfamide, cisplatin; ADOC, doxorubicine, cisplatin, vincristine, cyclophosphamide.

patients classified as no changes in reality experienced some tumor shrinkage but did not make it to be considered a partial remission according to the RECIST criteria. In Table 4 the actual percentage of tumor shrinkage in these patients has been added. No patient progressed on induction chemotherapy.

Palliative Chemotherapy for Advanced or Recurrent Thymoma

Thirteen patients received chemotherapy for palliation. In this group, 5 patients experienced a recurrence after an

operation (4 patients) or after radiotherapy for locally advanced thymoma and SVC syndrome (1 patient). The recurrences were diagnosed a mean of 6.8 years after the initial local treatment (range, 17 months to 15 years). The rest of the patients presented with metastatic disease (Table 5). All patients received platinum based chemotherapy and VIP was given to 7 patients. One patient died of respiratory insufficiency after the second VIP chemotherapy, related to an infection and complicated by myasthenia gravis. Her response could not be evaluated. The response rate to chemotherapy in this group of patients was 31% (4 out of 13).

The response to chemotherapy in the neoadjuvant setting was higher than in the advanced setting (Table 6). Furthermore, patients with metastases at start of chemotherapy had a lower response rate than those without metastases (6 out of 21 versus 6 out of 8). Interestingly the response rate in female was greater than in males (9 out of 13 versus 3 out of 16). None of the other clinical characteristics had influence on response to chemotherapy, including histology.

Tolerance to Therapy

There were 2 patients who died for reasons related to the treatment; both had myasthenia gravis: 1 patient, who underwent also right-sided pneumonectomy for extensive metastases on the visceral pleura, died of ARDS, and the other had an infectious complication following chemotherapy. A third patient, aged 77 developed severe leukothrombocytopenia and sepsis after the second cycle of VIP, despite the use of prophylactic G-CSF. She was admitted to the intensive care unit and eventually recovered. The other patients tolerated therapy relatively well, with the exception of the known toxicities of the regimens employed. There were no other severe adverse events related to surgery or to radiotherapy.

Treatment After First Line

A variety of therapies have been attempted in patients who relapsed after first line systemic therapy. Objective responses were only seen with the combination of octreotide and prednisone[15] in 2 out of 4 patients treated. All chemotherapy failed to induce durable responses. The experimental tyrosine kinase inhibitor SU 14813 (an inhibitor of VEGFR, among others) induced a prolonged stabilization of 1 year in 1 patient with a B3 thymoma.

Survival

Median follow-up from diagnosis was 47 months (range, 2–222 months). Median survival from diagnosis was 125 months. Significantly longer survival was observed in patients with earlier stages: median survival of stage IVB was 20 months, versus 132 of the other stages combined (P = 0.0006). Thymic carcinomas also had a poorer prognosis than the rest of the histologies combined (19 months versus 132 median survival, P = 0.0087). Age and gender did not influence survival.

Median follow-up from start of chemotherapy was 44 months (range, 1–106 months). Median survival from start of chemotherapy was 35 months for the whole population. There was no difference in survival depending on the age, presence of a secondary tumor or a paraneoplastic syndrome. Although female did better than male, this did not reach statistical significance. Thymic carcinoma had a poorer survival than the rest of histologies; from start of chemotherapy the median survival of thymic carcinoma patients was 15 months and median survival was not reached, for the other histologies (P = 0.0326; Fig. 1). The stage was an important prognostic factor. In the whole population, stage III patients are all alive and therefore no median survival has been reached; there is a significant difference in survival between stage III (A + B) and IV (A + B) (P = 0.012, median not reached versus median 20 months). There was however, no significant difference in survival between stage IVA and IVB (Fig. 2A, B). The advanced group had a worse survival than the neoadjuvant group (median survival 20 months versus not-reached, P = 0.056). The presence of metastases was a significant poor prognostic factor (no metastases more than 80% alive at 5 years, compared with 20 months median for presence of metastases, including pleural deposits, P = 0.0121).

In the neoadjuvant group there was a significant difference in survival between stage III and IV (no stage III in the advanced group). The median survival of the stage IV was 37 months (=0.024). There was a difference between responders and nonresponders, but this did not reach significance (P = 0.080). The presence of metastases in this group was a poor prognostic factor but it did not reach significance (P = 0.12).

TABLE 6. Response by Type of Chemotherapy

Type of Chemotherapy	Partial Response	Stable Disease	Progression	Not Evaluable
Neoadjuvant (n = 16)	8	8	0	0
Palliative (n = 13)	4	7	1	1

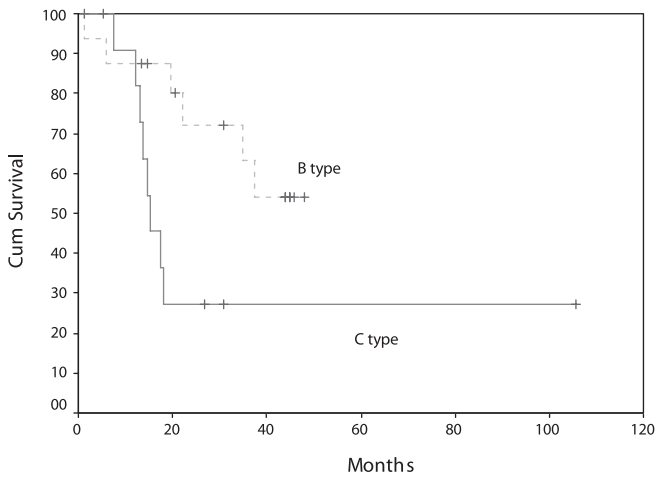

FIGURE 1. Survival from start of chemotherapy of patients with thymic carcinoma (WHO type C) versus thymomas (WHO type B). P = 0.0326.

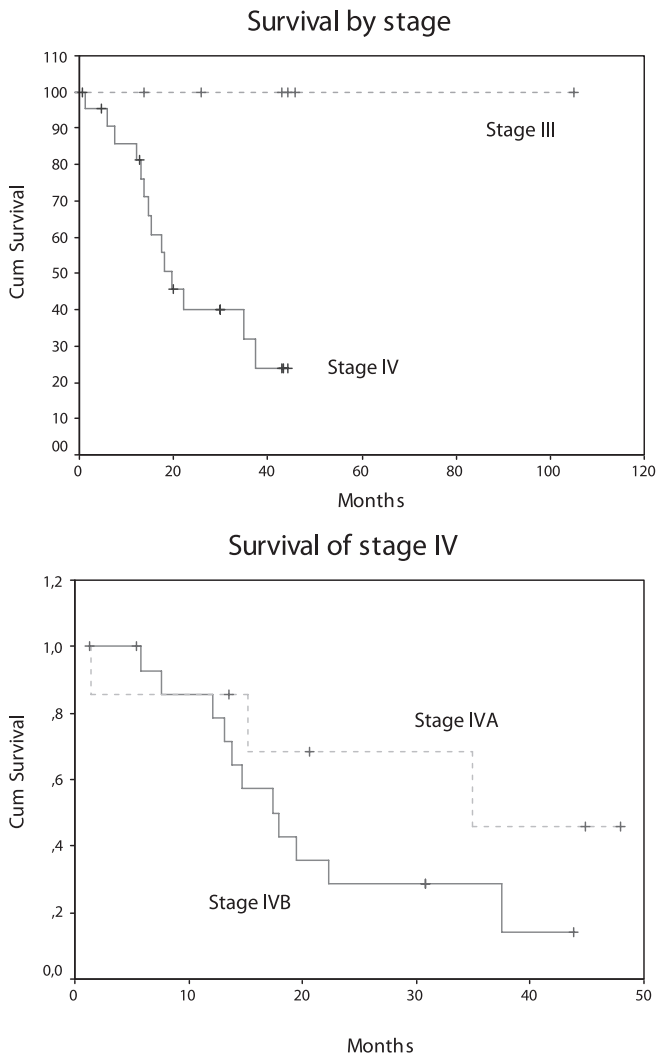

FIGURE 2. A, Survival from start of chemotherapy of stage III (A + B) versus stage IV (A + B); $P = 0.012$. B, Survival of stage IVA versus IVB.

The advanced disease group, where chemotherapy was given as palliation, showed no difference in survival between stage IVA and IVB. No difference in survival was seen between responders and nonresponders in advanced disease.

DISCUSSION

Over a period of 10 years, we identified 29 patients with thymoma treated with chemotherapy alone or in a combined modality approach. This is a large single institution series given the rarity of this tumor.

Patients included in this series were relatively advanced; among them were some patients who had a recurrence a long time following primary local therapy (mainly surgery), but most patients were diagnosed with advanced disease. A particularly high proportion of these patients presented with distant metastasis, a feature more common in thymic carcinomas than well-differentiated thymomas. The proportion of patients with thymic carcinoma was relatively large in our study. This may be caused partially because of the change in classifications but it may also reflect the referral pattern at our institution.

It is generally accepted that all patients whose tumors are potentially resectable should undergo surgical exploration and resection of their tumor.[5] Moreover, the staging of thymomas is essentially surgical, since invasion through the capsule is only reliably diagnosed by pathologic examination. In our series, surgery first was not possible because of the presence of large tumors or tumors encasing large vessels or invading the mediastinum.

The role of chemotherapy in patients with thymoma has been the topic of recent reviews.[9,16] Several chemotherapeutic agents have been used and combination chemotherapy has been shown to have a higher response rate than single agents.[17–19] The cisplatin-containing regimens appear to be the most active, with an overall response rate ranging from 50 to 80%. Combinations including anthracyclines, etoposide, and ifosfamide have been used rather extensively and the response rates to combination chemotherapy vary from series to series. Also, because this is a rare disease, series are usually rather small and no randomized trials comparing regimens are available. Combinations of cisplatin, ifosfamide, and etoposide (VIP),[13] cisplatin, doxorubicin, and cyclophosphamide (PAC)[20] and doxorubicin, cisplatin, vincristine, and cyclophosphamide (ADOC)[14] have been studied in prospective series of thymoma patients and have been shown to be effective regimens.[9]

At our institution, most patients were treated with VIP chemotherapy. This regimen was used as neoadjuvant, as adjuvant, and also as first-line treatment of recurrent disease. In general, the response rate to chemotherapy appeared lower than reported in previous studies. This may be a reflection of the poor prognostic group of patients that were treated. The majority of our patients had stage IV disease, and 12 patients had thymic carcinoma, which is known to be a more aggressive tumor than better differentiated thymomas.[21] The relatively low response rate to chemotherapy in our study may possibly also be because of the strict use of the RECIST criteria and it is possible that older series used less strict criteria for response. However, it is noteworthy that all patients in the neoadjuvant group experienced some tumor reduction, although this did not qualify as partial remission in many cases. In a study of 22 patients with better differentiated thymomas and less advanced stages, a response rate of 77% was obtained with cyclophosphamide, doxorubicin, cisplatin, and prednisone.[22] Conversely, a phase II study of VIP in 34 patients with advanced disease, not amenable to local treatment, obtained a response rate of 32%,[13] which is in line with the results we obtained in our series. Given the toxicity of the VIP regimen and the relative inferior response rate, the VIP regimen should probably not be employed in first-line treatment of this disease.

Although thymomas are tumors sensitive to chemotherapy, thymic carcinomas appear less sensitive to chemotherapy and response to chemotherapy is of shorter duration.[19,23,24] In

our study, however, we could not identify a different response to chemotherapy depending on histology. Interestingly, however, our patients with thymic carcinoma had a significantly worse survival than the thymoma patients, despite a similar response to chemotherapy. For thymic carcinomas the involvement of great vessels and radical resectability are the most important prognostic factors.[25] In a large review of 1320 thymic epithelial tumors from Japan, treated in 115 institutes between 1990 and 1994, 5-year survival of thymic carcinoma patients was 67%, 30% and 24% for radically resected, debulked, and inoperable groups, respectively.[26] In this series, a total of 182 thymic carcinomas were reported, of which only 50% were radically operable. Multimodality treatment is responsible for most long term survivors with thymic carcinomas.[27,28] A correlation appeared to be present between stage and histologic type in a retrospective series of 130 resected patients, and B3 cases had more advanced stages.[29]

Certainly there is room for improvement of systemic therapy results in this disease. A better understanding of the biology of these tumors is needed to develop better agents and agents more specifically targeted to molecular defects exquisitely present in these tumors.[30] Patients who recurred after first-line chemotherapy in this study received a number of second-line chemotherapy regimens and novel targeted agents. A recently published phase II trial in 42 patients with octreotide scan-positive patients with thymic tumors demonstrated modest activity of octreotide alone (10.5%) in patients with advanced thymoma, and a response of 30.3% with the addition of prednisone; no responses were observed in 'non-pure' thymomas.[15] Another study of 16 heavily pretreated patients with thymoma or thymic carcinoma demonstrated a response rate of 37% with the combination. There was one patient with thymic carcinoma who showed a partial response.[31] In our patients, octreotide with prednisone was the only treatment that produced objective remissions after first-line chemotherapy in 2 out of 4 patients treated, but the response was of short duration.

Another new therapeutic option is the use of tyrosine kinase inhibitors. The epidermal growth factor receptor (EGFR) is expressed in a high percentage of invasive thymomas, whereas c-kit has been shown to be expressed in thymic carcinomas.[32,33] Thymomas are generally EGFR positive/c-KIT negative, and EGFR negative/c-KIT positive staining is typical for thymic carcinoma. We treated 2 patients with gefitinib, but no major response was obtained. We also treated 2 patients with imatinib, based on the high c-kit expression in these tumors, but neither showed a benefit. A recent case report was published of a patient with a c-kit mutated thymoma who responded to imatinib.[34] Unfortunately, it appears that most thymomas do not have mutations of the c-kit gene.[35]

In conclusion, the results of combined modality therapy in thymic malignancies are reasonably good in less advanced cases. Occasional metastatic cases may be treated successfully with aggressive combined modality approaches. Chemotherapy in the palliative setting has modest efficacy and the search for targeted therapies in this rare tumor type is warranted.

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