VOLUME 29 · NUMBER 15 · MAY 20 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Study of Carboplatin and Paclitaxel in Advanced Thymoma and Thymic Carcinoma

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See accompanying article on page 2052

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Submitted September 30, 2010; accepted February 11, 2011; published online ahead of print at www.jco.org on April 18, 2011.

Supported by Grant No. CA-23318 from the National Cancer Institute, Bethesda, MD.

Presented in part at the 44th Annual Meeting of the American Society of Clinical Oncology, May 30-June 3, 2008, Chicago, IL.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/11/2915-2060/$20.00

DOI: 10.1200/JCO.2010.32.9607

ABSTRACT

Purpose
The purpose of this study was to evaluate the impact of carboplatin and paclitaxel in patients with advanced previously untreated thymoma and thymic carcinoma.

Patients and Methods
We conducted a prospective multicenter study in patients with unresectable thymoma (n = 21) or thymic carcinoma (n = 23). Patients were treated with carboplatin (area under the curve, 6) plus paclitaxel (225 mg/m^2) every 3 weeks for a maximum of six cycles. The primary end point of this trial was to evaluate the objective response rate.

Results
From February 2001 through January 2008, 46 patients were enrolled. Thirteen patients had grade 4 or greater toxicity, mostly neutropenia. Using RECIST (Response Evaluation Criteria in Solid Tumors) 1.0 criteria, three complete responses (CRs) and six partial responses (PRs; objective response rate [ORR], 42.9%; 90% CI, 24.5% to 62.8%) were observed in the thymoma cohort; 10 patients had stable disease. For patients with thymic carcinoma, no CRs and five PRs (ORR, 21.7%; 90% CI, 9.0% to 40.4%) were observed; 12 patients had stable disease. Progression-free survival (PFS) was 16.7 (95% CI, 7.2 to 19.8) and 5.0 (95% CI, 3.0 to 8.3) months for thymoma and thymic carcinoma cohorts, respectively. To date, only seven patients (33.3%) with thymoma have died, compared with 16 patients (69.6%) with thymic carcinoma. Median survival time was 20.0 months (95% CI, 5.0 to 43.6 months) for patients with thymic carcinoma, but it has not been reached for patients with thymoma.

Conclusion
Carboplatin plus paclitaxel has moderate clinical activity for patients with thymic malignancies, but this seems less than expected with anthracycline-based therapy. Patients with thymic carcinoma have poorer PFS and overall survival than patients with thymoma.

J Clin Oncol 29:2060-2065. © 2011 by American Society of Clinical Oncology

INTRODUCTION

Thymoma and thymic carcinoma are rare tumors, with an annual incidence of 1.5 per 1 million person-years. However, they represent the most common neoplasm of the anterior mediastinum. Thymic carcinoma accounts for 5% of all thymic malignancies.[1,2] Thymomas are typically discovered in routine radiographs or during evaluation for myasthenia gravis. In most cases, tumors are localized and treated by surgical resection.

About one third of patients with thymoma and two thirds with thymic carcinoma are diagnosed with locally advanced disease or distant metastases or recurrent disease after primary therapy.[3-6] In such cases, multimodality therapy with surgery, radiation, and chemotherapy may be indicated.[7-11] Both thymoma and thymic carcinoma are reported to have a similar cell of origin, and both are sensitive to a broad range of single agents, including platins and paclitaxel, as well as combination regimens.[12,13] Anthracycline-based regimens with cisplatin, doxorubicin, and cyclophosphamide (PAC) have produced an objective response rate (ORR) of 55% to 90% and 5-year survival of 30% to 55%.[7-9] However, anthracyclines are associated with cardiomyopathy and heart failure, and these effects are more likely when it is administered concurrently with radiation treatment. In those patients who are receiving radiation therapy, nonanthracyline regimens would be preferable to minimize potential adverse effects.

With this in mind, the Eastern Cooperative Oncology Group (ECOG) initiated a prospective

multicenter study in previously untreated patients with advanced thymic cancers using carboplatin and paclitaxel. The primary end point of the trial was objective response rate, with secondary end points of duration of response, progression-free survival (PFS), overall survival (OS), and toxicity.

PATIENTS AND METHODS

Patients

Eligible patients were age 18 years or older with histologically confirmed invasive, recurrent, or metastatic thymoma or thymic carcinoma not amenable to potentially curative therapy by surgery, with disease measurable in at least one dimension on radiographic studies. All eligible patients were required to have an ECOG performance status of 0 or 1, adequate bone marrow reserve (with granulocyte count $\geq$ 1,500 cells/μL and platelet count of $\geq$ 100,000 cells/μL), renal function (creatinine $\leq$ 2.0 mg/dL), and hepatic function (serum bilirubin $\leq$ 1.5 mg/dL). Patients were not eligible if they had prior malignancies, unless curatively treated with no evidence of recurrence within the previous 5 years. Those patients who had previously received preoperative or adjuvant chemotherapy for thymic malignancy were allowed to enroll, if disease-free survival before recurrence was longer than 1 year. All patients signed a written informed consent before study entry.

Treatment Regimen

Patients received paclitaxel 225 mg/m^2 intravenously (IV) over 3 hours followed by carboplatin at an area under the curve of 6 IV over 30 minutes on day 1. All patients were premedicated with cimetidine (300 mg), diphenhydramine (25 mg), and dexamethasone (20 mg) IV 1 hour before the paclitaxel infusion. Treatments were repeated every 21 days for two courses in the absence of disease progression. Patients without unacceptable toxicity or progressive disease received four additional courses of therapy for a maximum of six courses. Treatment beyond six courses was administered at the discretion of the treating physician. Patients were evaluated with chest computed tomography (CT) scan, as indicated, every 3 months for 2 years, every 6 months for 3 years, and then annually.

Evaluation

Pretreatment evaluation included history and physical examination, complete blood count and metabolic profile, CT scan of the chest and abdomen, and pregnancy test (in women of child-bearing age). Evaluation during treatment included history and physical examination, including assessment of toxicity and complete blood count and chemistry before each cycle. Disease assessment was accomplished with a CT scan after the second and fourth cycles and at the end of treatment.

Design and Statistical Analysis

A two-stage design was employed to estimate the number of patients required in each stratum. For the thymoma cohort, a true ORR of 60% was considered worthy of additional study, whereas a response rate of 40% was not of interest. For this cohort, 25 patients were to be accrued in the first stage. If 10 or more responses were observed among the initial 22 eligible patients, 20 additional patients were to be entered, assuming 18 would be eligible. This regimen was considered worthy of additional study if at least 21 responses were observed among the overall 40 eligible patients who started protocol treatment. For the thymic carcinoma cohort, a true ORR of 45% was considered worthy of additional study, whereas a response rate of 20% was not of interest. For this cohort, 10 patients were to be accrued in the first stage. If two or more responses were observed among the initial nine eligible patients, 13 additional patients were to be registered, assuming 11 would be eligible. This regimen was considered worthy of additional study if seven or more responses were observed among the overall 20 eligible patients who started protocol treatment.

This analysis was based on ECOG 1C99 data pulled on September 8, 2009. All eligible and treated patients were included in the response and survival analyses. All treated patients were included in the toxicity analysis.

The primary end point of this trial was to evaluate ORR (complete response [CR] and partial response [PR]) to carboplatin plus paclitaxel in patients with thymic malignancies. Secondary end points included the duration of response, PFS, and OS. Response was evaluated using RECIST (Response Evaluation Criteria in Solid Tumors) 1.0 criteria. Response duration was measured from date of first documented response until relapse. Patients with responses but without documented disease progression were censored at time of last disease evaluation. OS was defined as time from registration to death as a result of any cause. Patients who were alive at the time of this analysis were censored at date last known to be alive. PFS was defined as time from registration to first documentation of disease progression or death. Patients without documented progression were censored at time of last disease assessment.

Descriptive statistics were used to characterize patient characteristics and adverse events (assessed using CTC [Common Toxicity Criteria] version 2.0). Fisher's exact and Wilcoxon tests were used to evaluate differences in patient characteristics. Exact binominal 90% CI was computed for ORR. Event-time distributions were plotted using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards models were used to estimate hazard ratios and test for significance for survival. All *P* values are two sided, and a level of 5% was considered statistically significant, unless otherwise specified.

RESULTS

Forty-six patients were enrolled onto the trial from February 2001 through January 2008. At time of first-stage response evaluations, patients were classified according to several histologic classifications that stratified patients into either thymoma or thymic carcinoma groups. Patients' histologic material was subsequently reviewed by one of the authors (S.C.A.) and later reclassified according to 2004 WHO classification.[14] The first-stage response criterion for the thymoma stratum was not met; this stratum was thus closed early, after 25 patients were enrolled with an entry diagnosis of thymoma. The first-stage response criterion for patients with thymic carcinoma was met, so this stratum proceeded to the second stage of accrual without suspension; it closed at the end of the second stage with 21 patients enrolled with an entry diagnosis of thymic carcinoma.

One patient withdrew consent and never received chemotherapy, and a second patient was ineligible because after receiving eight cycles of chemotherapy, he underwent surgical resection, with a finding of teratoma (and was thus felt to have a primary germ-cell tumor). This left 44 patients in the primary analysis and 45 patients in the toxicity analysis.

At the time of data analysis for this article, updated information regarding WHO classification was available (Table 1). In this analysis,

Table 1. WHO Classification of Patients With Thymic Neoplasms

WHO Classification	Thymic Tumor	
	No.	%
A	1	2.3
AB	1	2.3
B1	8	18.1
B2	7	15.9
B3	10	22.7
C	13	29.6
Thymoma-NOS*	4	9.1

*Thymoma-NOS classification indicates not otherwise specified because of limited material.

Table 2. Patient Characteristics

Characteristic	Thymoma (n = 21)		Thymic Carcinoma (n = 23)		Total (N = 44)	
	No.	%	No.	%	No.	%
Age, years						
Median	50		50		50	
Range	32-76		20-67		20-76	
Sex						
Male	13	61.9	14	60.9	27	61.4
Female	8	38.1	9	39.1	17	38.6
Race						
White	14	66.7	14	60.9	28	63.6
Black	4	19.0	7	30.4	11	25.0
Other	3	14.3	2	8.7	5	11.4
ECOG PS						
0	11	52.4	8	34.8	19	43.2
1	10	47.6	15	65.2	25	56.8
Stage[15]						
III	3	14.3	4	17.4	7	15.9
IVa	14	66.7	8	34.8	22	50.0
IVb	4	19.0	11	47.8	15	34.1
Prior therapy						
Radiotherapy	4	19.0	4	17.4	8	18.2
Chemotherapy	1	4.8	0	0.0	1	2.3

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

patients with WHO classifications B3 and C were grouped together and labeled as the thymic carcinoma cohort (n = 23); all others (classifications A, AB, B1, B2, and thymoma-NOS) were grouped together and labeled as the thymoma cohort (n = 21). To have a valid conclusion, the following results were analyzed and reported based on the real histology in terms of WHO classification.

Patient Characteristics

Patient characteristics by stratum are listed in Table 2. Twenty-seven patients were male, and 17 were female. Nineteen had an ECOG performance status of 0, and the other 25 had a performance status of 1. One patient with thymoma had received prior preoperative chemotherapy. Eight had received prior radiation therapy. Nineteen percent of patients with thymoma had stage IVb disease at presentation, whereas 47.8% of patients with thymic carcinoma presented with stage IVb disease. The most common sites of metastasis were the lungs and pleura. Five patients (23.8%) in the thymoma group had myasthenia gravis or other autoimmune disease, compared with none in the thymic carcinoma group. No statistically significant difference between the two cohorts was observed in age, sex, race, performance status, or disease stage at registration.

Treatment Response

Forty-four patients were assessed for clinical outcome. Forty-nine percent of patients (21 of 43; no treatment information for one patient) completed at least six of the intended cycles of chemotherapy without interruption of therapy. The main reasons for discontinuation of treatment were toxicity or clinical deterioration (approximately 21%), patient withdrawal after four or more cycles (9%), and disease progression (12%). Among patients with thymoma, three achieved CR, and six achieved PR, resulting in an ORR of 42.9% (90% CI, 24.5% to 62.8%). Ten patients had stable disease. Of note, the one patient who had received prior chemotherapy had stable disease as best response to the study therapy. For patients with thymoma, no significant differences among various histologies were noted with respect to objective responses (A/AB *v* B1/B2 *v* thymoma-NOS; $P = .49$), but the numbers were not large enough to make meaningful conclusions. Median PFS in patients with thymoma was 16.7 months (95% CI, 7.2 to 19.8 months), and median OS was not reached after 59.4 months of median follow-up. Median duration of response was 16.9 months (95% CI, 3.1 to 22.0 months). At the time of this analysis, seven of the 21 patients (33%) with thymoma had died.

Among patients with thymic carcinoma, there were no CRs. Five patients with thymic carcinoma achieved PR, and 12 patients had stable disease (ORR, 21.7%; 90% CI, 9.0% to 40.4%). Median PFS was 5 months (95% CI, 3.0 to 8.3 months), and median OS was 20.0

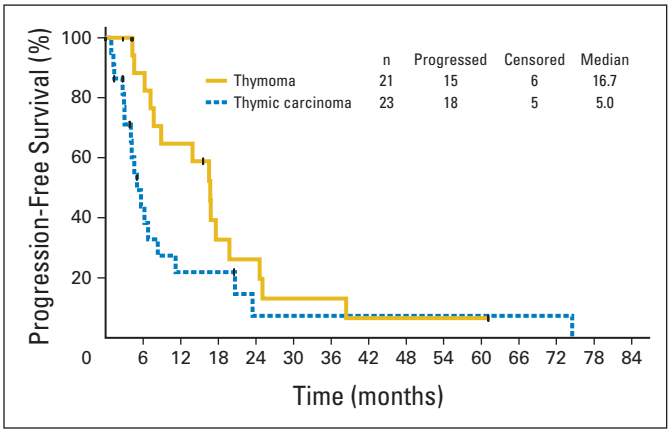

Fig 1. Progression-free survival in patients with thymoma and thymic carcinoma.

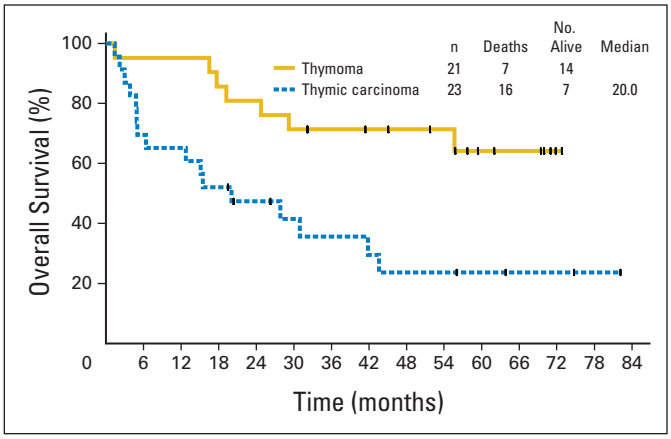

Fig 2. Overall survival in patients with thymoma and thymic carcinoma.

months (95% CI, 5.0 to 43.6 months). Median duration of response was 4.5 months (95% CI, 3.4 to 9.9 months). Sixteen of the 23 patients with thymic carcinoma had died at the time of this data analysis.

Figure 1 shows the PFS curve for thymoma and thymic carcinoma, and Figure 2 shows the OS curve for the two cohorts together. The figures demonstrate that patients with thymoma have marginally improved PFS (log-rank $P = .06$) and OS (log-rank $P = .01$), compared with patients with thymic carcinoma. Cox regression analysis shows that the hazard ratio of thymic carcinoma over thymoma is 3.0 (95% CI, 1.2 to 7.8; $P = .02$) and 2.1 (95% CI, 1.0 to 4.5; $P = .06$) for OS and PFS, respectively, adjusting for disease stage at registration, sex, performance status, and prior radiation therapy. Although not part of the study design, five patients underwent surgery after chemotherapy. Two of these five patients remained progression free at more than 15 and more than 74 months, respectively, from time of surgery; one patient subsequently relapsed and died.

Toxicity

The principal toxicity was bone marrow suppression with grade 4 neutropenia observed in 24.4% of patients. One patient had grade 3 febrile neutropenia, and one had grade 4. Grade 3 sensory neuropathy was seen in 13.3% of patients; otherwise, the remainder of toxicities noted were either grade 1or 2. There was no cardiotoxicity. One patient developed acute nonlymphocytic leukemia approximately 14 months after completing therapy.

DISCUSSION

In this trial, carboplatin and paclitaxel resulted in ORRs of 42.9% and 21.7% in patients with thymoma and thymic carcinoma, respectively, with a median follow-up of 59.4 months (95% CI, 41.4 to 69.9 months) and 63.8 months (95% CI, 20.3 to 82.2 months), respectively. Median OS was not reached for patients with advanced thymoma, whereas it was only 20.0 months in patients with thymic carcinoma. Similarly, patients with thymoma seemed to have better PFS and OS than patients with thymic carcinoma (Figs 1 and 2). Possible explanations for these findings are differing tumor biology for these thymic tumors; additionally, most of the patients with thymic carcinoma had advanced stage IVb disease, compared with those in the thymoma group (48% *v* 19%).

Per study protocol, if at least 10 responses were observed among 22 eligible and treated patients with thymoma enrolled during the first stage, this stratum would proceed to the second stage of accrual. In our study, we observed nine of 21 eligible and treated patients with thymoma (in terms of WHO classification) during the first stage. Because we were short of one patient with thymoma in our first-stage accrual, and we were lagging in one response only, no definite answer can be drawn based on the number of objective responses. Nevertheless, the response rate of 42.9% in patients with thymoma is close to the null hypothesis of 40%. Although the 90% CI of 24.5% to 62.8% for the ORR of 42.9% barely includes a true response rate of 60%, the wide CI might have resulted from the small number of patients in this cohort, and a rate of 60% cannot be ruled out. It is thus concluded that there is limited evidence to support additional investigation of carboplatin plus paclitaxel as treatment for advanced thymoma.

In the thymic carcinoma cohort, if at least seven responses were observed among the 20 total eligible and treated patients, this therapy would be considered worthy of additional study. However, only five of 23 patients with thymic carcinoma demonstrated objective responses, and the 90% CI of 9.0% to 40.4% for the ORR of 21.7% in the thymic carcinoma cohort is not consistent with a true response rate of 45%.

Table 3. Combination Chemotherapy for Advanced Thymoma/Thymic Carcinoma

Study	Regimen	No.	CR (%)	PR (%)	ORR (%)	MST (months)
Fornasiero et al[7]	ADOC	37	43	48	91.8	15
Loehrer et al[8]	PAC	30	10	40	50	37.7
Loehrer et al[9]	PAC	23	22	48	70	93
Macchiarini et al[15]	PEpE	7	28.6	71.4	100	NS
Kim et al[11]	CAPP	22	14	63	77	NS
Giaccone et al[16]	PE	16	31	25	56	51.6
Loehrer et al[17]	VIP	28	0	32	32	31.6
Igawa et al[18]	Car/Pac	11	0	4	36	22.7
Current study	Car/Pac					
Thymoma		21	14.3	28.6	42.9	NR
Thymic carcinoma		23	0	21.7	21.7	20.0

Abbreviations: CR, complete response; PR, partial response; ORR, objective response rate; MST, median survival time; ADOC, doxorubicin, cisplatin, vincristine, cyclophosphamide; PAC, cisplatin, doxorubicin, cyclophosphamide; PEpE, cisplatin, epirubicin, etoposide; CAPP, cyclophosphamide, doxorubicin, cisplatin, prednisone; PE, cisplatin, etoposide; VIP, etoposide, ifosfamide, cisplatin; Car/Pac, carboplatin, paclitaxel; NS, not stated; NR, not reached after 59.4 months of median follow-up.

These data support the conclusion that carboplatin plus paclitaxel is not a preferred regimen for advanced thymic carcinoma.

Anthracycline-based regimens have been a standard of care for thymic malignancies based on various phase II clinical trials (Table 3). Fornasiero et al[7] reported their 13 years of experience with 37 patients with stage III and IV thymoma who were treated with cisplatin, doxorubicin, vincristine, and cyclophosphamide combination chemotherapy. The overall response rate was 91.8%, with 43% of patients achieving complete remission, but median survival time was only 15 months. Loehrer et al[8] reported a 50% overall response rate (CR, 10%) and median survival time of 37.7 months an intergroup trial in which 29 patients with thymoma and one patient with thymic carcinoma with metastatic or locally progressive recurrent disease were treated with PAC. In another phase II study using a multidisciplinary approach with induction chemotherapy followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable thymomas conducted by Kim et al,[11] 22 patients received induction chemotherapy with PAC plus prednisone for three cycles. The authors reported that induction chemotherapy produced 14% CR and 63% PR rates.

Anthracyclines are known to be associated with cardiomyopathy, especially when combined with radiotherapy. Because thymic cancers often occur in older patients, use of anthracyclines may be limited in this population because of cardiac history and possible need for radiotherapy. Therefore, nonanthracycline regimens may be preferable for this group of patients. One such study was conducted by the European Organisation for Research and Treatment of Cancer, in which 16 patients with advanced or recurrent thymoma were treated with cisplatin and etoposide. In this trial, there were five CRs and four PRs (overall ORR, 56%).[16] On the basis of the single-agent activity of ifosfamide in thymoma,[14,19] 20 patients with advanced thymoma and eight patients with thymic carcinoma were treated with etoposide, ifosfamide, and cisplatin in an intergroup trial conducted by ECOG. An ORR of 35% and 25%, all PRs, was reported in patients with thymoma and thymic carcinoma, respectively. Grassin et al[20] had similarly poor results (PR, 25%) in 16 patients treated with etoposide, ifosfamide, and cisplatin. Both of these cisplatin/etoposide-based regimens produced response rates that seem inferior to those in previously mentioned reports with anthracycline-based regimens.[17] Various case reports and at least one retrospective study have demonstrated that paclitaxel, either as a single agent or in combination with carboplatin, has activity in thymoma and thymic carcinoma.[18,21-23] The present study supports this notion. However, collectively with other regimens not using anthracyclines, the ORRs are consistently lower than those with regimens that do contain anthracyclines.

Thymic carcinoma is considered by some to be on a continuum with thymoma, with features of all tumor types seen in some patients, but it is rarely associated with paraneoplastic disorders, demonstrates distant hematogenous metastasis more frequently, and has a different expression for epidermal growth factor receptor and c-kit ligand than thymoma.[15,24,25] Because most patients with thymic carcinoma present with unresectable disease, this histology is associated with poor prognosis.[26]

In summary, our study is one of the largest prospective multicenter trials conducted to date in advanced thymoma and thymic carcinoma. It shows that the combination of carboplatin and paclitaxel has modest activity, but it seems inferior to previously published results for anthracycline-based chemotherapy. A slightly lower response rate was also observed when compared with the combination of cisplatin and etoposide, which could suggest that carboplatin is inferior to cisplatin in treating this disease; however, an early phase II trial of single-agent cisplatin showed a response rate of only 10% in thymoma.[12]

Given the rarity of these tumors, prospective randomized trials are unlikely to be performed in the future. Cumulative data, however, would suggest that anthracycline-based regimens should remain a standard of care in this group of patients (without clinical contraindications for anthracyclines) outside a clinical trial. For those patients who cannot tolerate anthracyclines, carboplatin plus paclitaxel can be considered as a reasonable alternative. Additionally, this article supports the hypothesis that thymoma and thymic carcinoma seem to be distinct clinical entities, and future trials should clearly separate these populations.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** David H. Johnson, Mirna Therapeutics (C) **Stock Ownership:** None **Honoraria:** None **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

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Final approval of manuscript: All authors

REFERENCES

1. Engels EA, Pfeiffer RM: Malignant thymoma in the United States: Demographic patterns in incidence and associations with subsequent malignancies. Int J Cancer 105:546-551, 2003
2. Mullen B, Richardson JD: Primary anterior mediastinal tumors in children and adults. Ann Thorac Surg 42:338-345, 1986
3. Laurent F, Latrabe V, Lecesne R, et al: Mediastinal masses: Diagnostic approach. Eur Radiol 8:1148-1159, 1998
4. Verstandig AG, Epstein DM, Miller WT Jr, et al: Thymoma: Report of 71 cases and a review. Crit Rev Diagn Imaging 33:201-230, 1992
5. Wilkins EW Jr, Grillo HC, Scannell JG, et al: J. Maxwell Chamberlain memorial paper: Role of

staging in prognosis and management of thymoma. Ann Thorac Surg 51:888-892, 1991

6. Souadjian JV, Enriquez P, Silverstein MN, et al: The spectrum of diseases associated with thymoma: Coincidence or syndrome? Arch Intern Med 134:374-379, 1974

7. Fornasiero A, Daniele O, Ghiotto C, et al: Chemotherapy for invasive thymoma: A 13-year experience. Cancer 68:30-33, 1991

8. Loehrer PJ, Kim K, Aisner SC, et al: Cisplatin plus doxorubicin plus cyclophosphamide in metastatic or recurrent thymoma: Final results of an intergroup trial—The Eastern Cooperative Oncology Group, Southwest Oncology Group, and Southeastern Cancer Study Group. J Clin Oncol 12:1164-1168, 1994

9. Loehrer PJ, Chen M, Kim K, et al: Cisplatin, doxorubicin, and cyclophosphamide plus thoracic radiation therapy for limited-stage unresectable thymoma: An intergroup trial. J Clin Oncol 15:3093-3099, 1997

10. Berruti A, Borasio P, Gerbino A, et al: Primary chemotherapy with adriamycin, cisplatin, vincristine and cyclophosphamide in locally advanced thymomas: A single institution experience. Br J Cancer 81:841-845, 1999

11. Kim ES, Putnam JB, Komaki R, et al: Phase II study of a multidisciplinary approach with induction chemotherapy, followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas: Final report. Lung Cancer 44:369-379, 2004

12. Bonomi PD, Finkelstein D, Aisner S, et al: EST 2582 phase II trial of cisplatin in metastatic or recurrent thymoma. Am J Clin Oncol 16:342-345, 1993

13. Umemura S, Segawa Y, Fujiwara K, et al: A case of recurrent metastatic thymoma showing a marked response to paclitaxel monotherapy. Jpn J Clin Oncol 32:262-265, 2002

14. Muller-Hermelink HK, Engel P, Kuo TT, et al: Tumors of the thymus, in Travis WD, Brambilla E, Hermelink HK, et al (eds): Pathology and Genetics: Tumors of the Lung, Pleura, Thymus and Heart—WHO Classification of Tumors. Lyon, France, IARC Press, 2004, pp 145-245

15. Macchiarini P, Chella A, Ducci F, et al: Neoadjuvant chemotherapy, surgery, and postoperative radiation therapy for invasive thymoma. Cancer 68: 706-713, 1991

16. Giaccone G, Ardizzoni A, Kirkpatrick A, et al: Cisplatin and etoposide combination chemotherapy for locally advanced or metastatic thymoma: A phase II study of the European Organisation for Research and Treatment of Cancer Lung Cancer Cooperative Group. J Clin Oncol 14:814-820, 1996

17. Loehrer PJ Sr, Jiroutek M, Aisner S, et al: Combined etoposide, ifosfamide, and cisplatin in the treatment of patients with advanced thymoma and thymic carcinoma: An intergroup trial. Cancer 91: 2010-2015, 2001

18. Igawa S, Murakami H, Takahashi T, et al: Efficacy of chemotherapy with carboplatin and paclitaxel for unresectable thymic carcinoma. Lung Cancer 67:194-197, 2010

19. Highley MS, Underhill CR, Parnis FX, et al: Treatment of invasive thymoma with single-agent ifosfamide. J Clin Oncol 17:2737-2744, 1999

20. Grassin F, Paleiron N, André M, et al: Combined etoposide, ifosfamide, and cisplatin in the treatment of patients with advanced thymoma and thymic carcinoma: A French experience. J Thorac Oncol 5:893-897, 2010

21. Umemura S, Segawa Y, Fujiwara K, et al: A case of recurrent metastatic thymoma showing a marked response to paclitaxel monotherapy. Jpn J Clin Oncol 32:262-265, 2002

22. Jan N, Villani GM, Trambert J, et al: A novel second line chemotherapy treatment of recurrent thymoma. Med Oncol 14:163-168, 1997

23. Maruyama R, Suemitsu R, Okamoto T, et al: Persistent and aggressive treatment for thymic carcinoma: Results of a single-institute experience with 25 patients. Oncology 70:325-329, 2006

24. Masaoka A, Monden Y, Nakahara K, et al: Follow-up study of thymomas with special references to their clinical stages. Cancer 48:2485-2492, 1981

25. Suster S, Moran CA: Thymoma, atypical thymoma, and thymic carcinoma. Am J Clin Pathol 111:826-833, 1999

26. Kondo K, Monden Y: Therapy for thymic epithelial tumors: A clinical study of 1,320 patients from Japan. Ann Thorac Surg 76:878-884, 2003

