

Cisplatin, Doxorubicin, and Cyclophosphamide Plus Thoracic Radiation Therapy for Limited-Stage Unresectable Thymoma: An Intergroup Trial

By Patrick J. Loehrer, Sr, Michael Chen, KyungMann Kim, Seena C. Aisner, Lawrence H. Einhorn, Robert Livingston, and David Johnson

Purpose: To determine the response rate of cisplatin plus doxorubicin plus cyclophosphamide (PAC) in patients with limited-stage unresectable thymoma. In addition, this study was undertaken to determine the toxicity, progression-free survival, and overall survival of combined-modality therapy with PAC plus radiation therapy.

Patients and Methods: Patients with a histologic diagnosis of limited-stage unresectable thymoma or thymic carcinoma were eligible. Further requirements included a Karnofsky Performance Score of > 60, no prior radiation to the chest, and adequate bone marrow, hepatic, and renal function. No patient had undergone chemotherapy previously. Patients received two to four cycles (repeated every 3 weeks) of cisplatin (50 mg/m²), doxorubicin (50 mg/m²), and cyclophosphamide (500 mg/m²) followed by a total dosage of 54 Gy to the primary tumor and regional lymph nodes for patients with a stable, partial, or complete response to chemotherapy.

Results: From November 1983 through January 1995, 26 patients were entered onto the trial. Three pa-

tients were ineligible on the basis of pathologic review (lung cancer, germ cell cancer, lymphoma). Toxicity, primarily hematologic, was mild, with only one early death due to a perforated abdominal viscus. Among the 23 assessable patients, there were five complete and 11 partial responses to chemotherapy (overall response rate, 69.6%). The median time to treatment failure was 93.2 months (range, 3 to 99.2+ months), and the median survival time was 93 months (range, 1 to 110 months). The 5-year survival rate is 52.5%.

Conclusions: PAC combination chemotherapy produces response rates in the management of patients with limited thymoma. Combined-modality therapy is feasible and associated with prolonged progressive-free survival. The benefit of combined-modality therapy over radiation therapy alone is suggested for patients with unresectable thymoma.

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THYMOMA IS AN UNUSUAL neoplasm, but it represents one of the commonest tumors of the anterior mediastinum. In many patients, thymomas are discovered during an evaluation for myasthenia gravis or other paraneoplastic syndromes such as pure red cell aplasia or hypogammaglobulinemia. The majority of patients have an encapsulated or noninvasive tumor that can usually be resected for cure. Approximately one third of patients will have locally advanced or metastatic disease, for which radiation therapy or chemotherapy may play a role.¹⁻³ Radiation therapy has routinely been used for those patients with invasive disease or bulky mediastinal disease with obvious extension around vascular structures. Yet, 50% to 70% of such patients may still develop recurrent thymoma, which suggests a potential role for combined modality therapy.

Systemic chemotherapy is capable of producing durable remissions in patients with advanced or metastatic thymoma. The data supporting this have largely been in the case reports and small series. In one of the largest prospective trials, cisplatin plus doxorubicin plus cyclophosphamide (PAC) produced a 50% objective response rate (3 complete responses [CR], 12 partial responses [PR]) in 30 assessable patients with advanced thymoma.⁴ The 5-year survival rate was 32%. On the basis of preliminary data from this trial and others,^{5,6} a phase II trial was

designed to evaluate combined modality treatment for patients with limited but unresectable thymoma. This trial was initiated by the Southeastern Cancer Study Group (SECSG) and the Southwest Oncology Group (SWOG) and was later completed by the Eastern Cooperative Oncology Group (ECOG). The purpose of this trial was to confirm the activity of PAC combination chemotherapy and to assess the toxicity, duration of remission, and over-

From the Department of Medicine, Indiana University Medical Center, Indianapolis, IN; Department of Radiation Oncology, Mayo Clinic, Rochester, MN; Department of Pathology, UMDNJ, New Jersey Medical School, Newark NJ; Division of Medical Oncology, University of Washington, Seattle, WA; and Division of Medical Oncology, Vanderbilt University, Nashville, TN.

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Address reprint requests to Patrick J. Loehrer, Sr, MD, Section of Hematology/Oncology, Indiana University Medical Center, University Hospital 1730, 550 N University Blvd, Indianapolis, IN 46202-5265.

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all survival of PAC followed by radiation therapy in patients with localized but unresectable thymoma.

PATIENTS AND METHODS

From November 1983 through January 1995, 26 patients with limited-stage thymoma were entered onto this trial. The trial was initially coordinated by the SECSG from November 1983 through February 1985. At this time, the trial included patients with advanced disease who were undergoing chemotherapy only, as well as patients with limited-stage disease. Patients with limited-stage disease were defined as those with disease that could be encompassed within a single radiotherapy portal. Patients entered onto this trial with advanced disease have been previously reported.^{4,7}

When ECOG agreed to supervise this trial, it was decided to divide this study into two individual trials, including one for disseminated and one for limited-stage disease. Seven patients were entered onto this early phase of the trial before cessation of the SECSG/SWOG trial in February 1985. In May 1989, this phase II trial was reopened (within ECOG alone) for patients with limited unresectable thymoma. Nineteen patients were entered onto this latter phase of the trial.

Eligible patients included those with histologic proof of thymoma. Patients with thymic carcinoma were eligible but analyzed for response and survival separately. All patients were felt to have limited-stage unresectable disease that was bidimensionally measurable on radiographic studies. Patients were not eligible if they had a Karnofsky Performance Score of < 60, prior chemotherapy, previous radiation therapy to the mediastinum, another malignancy within the previous 5 years except for carcinoma in situ of the cervix, or history of congestive heart failure. All patients were required to have adequate bone marrow reserve (leukocytes $> 4 \times 10^9/L$; platelet counts $\geq 125 \times 10^9/L$), renal function (serum creatinine ≤ 2 mg/dL or creatinine clearance > 60 mL/min), and hepatic function (serum bilirubin ≤ 36 μ mol/L).

Pretreatment evaluation included history and physical examination, chest radiograph (posteroanterior and lateral [PAL]), complete blood count (CBC), serum electrolytes, and a chemistry panel that included tests of liver function and serum creatinine concentration determination. Computerized tomography of the chest was performed as indicated for tumor measurements. All patients provided written informed consent.

Evaluations during treatment included a history and physical examination, serum chemistry panel, CBC, and chest radiograph performed every 3 weeks before the initiation of each treatment cycle. Computerized tomography of the chest was performed as indicated to document the response or progression of disease. Serial cardiac examinations were not mandated as part of this study but left to the discretion of the investigator for symptomatic patients.

Treatment Regimen

Patients received the PAC regimen every 21 days for a total of two (SECSG/SWOG) or four (ECOG) cycles before the initiation of radiation therapy. The PAC regimen consisted of cisplatin (50 mg/m²), doxorubicin (50 mg/m²), and cyclophosphamide (500 mg/m²), all given by slow intravenous infusion. Hydration with at least 1 L of 0.9N saline administered over a minimum of 2 hours was given before treatment, with similar hydration after chemotherapy. Antiemetic regimens were left to the discretion of the investigator,

but the use of corticosteroids (except stable dosages for myasthenia gravis) was specifically discouraged.

Patients were evaluated after two cycles (SECSG/SWOG) and four cycles (ECOG) of therapy to determine their response before radiation therapy. Patients with complete or partial response and stable disease received definitive radiotherapy to the mediastinum and the involved field. Radiation therapy was to begin within 3 to 4 weeks of the last cycle of chemotherapy. In patients treated in the first phase of the study (SECSG/SWOG), a maximum of six additional cycles of PAC combination chemotherapy was administered after radiation therapy. Because only one of the seven patients entered onto the SECSG/SWOG trial received chemotherapy after radiation therapy as originally defined, the second phase (ECOG) trial was modified to give four cycles of PAC (total) chemotherapy, with all cycles administered before definitive radiotherapy.

Radiation treatment was administered with megavoltage equipment (Cobalt 60, ≥ 4 MeV X-rays) with a minimum treatment distance to axis of 80 cm. The primary tumor volume, mediastinal lymph nodes and bilateral hilar lymph nodes were irradiated to a total dose of 5,400 cGy with a daily dose of 180 cGy/day. The target volume, defined at the time of simulation and treatment planning, included the primary tumor with a 2-cm margin. Supraclavicular lymph nodes were not routinely treated unless it was necessary to encompass the primary tumor volume. The maximum dosage to the spinal cord was not to exceed 4,400 cGy (by use of oblique or lateral fields). The maximum dosage to normal lung outside of the primary anteroposterior/posteroanterior treatment volume was not greater than 1,500 cGy, and the maximum dosage to the entire heart did not exceed 3,500 cGy. Less than 50% of the heart could receive 4,000 cGy.

A complete response was defined as complete disappearance of all objective evidence of disease. A partial response was defined as a 50% or greater reduction in the sum of the products of perpendicular diameters of measurable lesions lasting at least 1 month. Progressive disease was measured as a 25% or greater increase in the sum of the products of diameters of measurable disease or new lesions.

Survival was measured from date of registration onto the study until the date of death (from all causes) or the date when patient was last known to be alive. Relapse duration was measured from the date of the first documented response until relapse or death. Time to treatment failure was measured from the time of registration until documented disease progression, relapse, or death. Survival curves were plotted using the Kaplan-Meier method.⁸

Patient Characteristics

Patient characteristics are listed in Table 1. Twenty-six patients were entered onto the trial (seven, first phase [SECSG/SWOG]; nineteen, second phase [ECOG]). Three patients were deemed ineligible because of histology (squamous cell carcinoma of the lung, germ cell neoplasm, and malignant lymphoma, respectively). Another patient was technically ineligible because the pretreatment measurement serum bilirubin concentration obtained > 2 weeks before entry into the study was included in the analysis (of note, previous and subsequent bilirubin determinations were within normal limits). There were 23 patients fully assessable for response and survival. All 26 patients entered were assessable for toxicity.

The median age of eligible patients was 54.2 years (range, 28 to 70 years), and the median ECOG performance score was 1 (range, 0 to 2). There was a slight predominance of men, and most patients were white (18 white, 4 black, and 1 Hispanic). Most patients had

Table 1. Characteristics of Assessable Patients

Characteristic	n (%)
Age (years)	
Median	54.2
Range	(28-70)
M/F	13:10
Median ECOG performance score (range)	1 (0-2)
Stage	
Masaoka staging system ⁹	
III	22
IV _B	1
Gett classification ¹⁵	
III _A	14
III _B	8
IV	1
Prior major debulking surgery	4 (17)
Volume of residual disease	
Minimum	1
Gross	22
Symptoms	
Respiratory infections	3 (12)
Change in cough	9 (35)
Chest pain	6 (23)
Dyspnea	6 (23)
Hoarseness	3 (12)
Myasthenia gravis	7 (27)
Other	12 (52)
Pathology	
Lymphocytic predominant	2 (9)
Mixed	7 (30)
Epithelial predominant	9 (39)
Thymic carcinoma	2 (9)
Thymoma not otherwise specified	3 (13)

prior thoracotomy, but only four patients had major debulking surgery (residual disease measured 10 to 20 cm² in maximum diameter), and four had undergone minor debulking attempts (residual disease measuring 27.5 to 144 cm²) before the initiation of therapy. All but one patient had gross (> 10 cm²) disease at the time of entry onto the study. All but two patients had stage III disease according to the Masaoka Staging System⁹ (Table 2), including five patients with probable local extension to the sternum. The one patient who may have only had stage II disease had multiple sites within the mediastinum that were considered not resectable by the surgeon. One patient had stage IV_B (supraclavicular adenopathy on the ipsilateral side).

Most patients presented with signs and symptoms of local tumor involvement, including chest and shoulder pain, dysphagia, dyspnea, and superior vena caval syndrome. Six patients had cytology-negative pleural effusions at presentation. Seven patients had a history of myasthenia gravis. Pathology review demonstrated that most patients had epithelial predominant or mixed tumors. Two patients had thymic carcinoma.

RESULTS

Toxicity and Late Effects

Toxicity was graded according to the Common Toxicity Criteria. The overall incidence of toxicities is listed in Table 3. Twenty-six patients underwent a total of 87 cycles of chemotherapy, with a median of four cycles (range, 1 to 7 cycles). Hematologic toxicity was the most frequently observed, but only three patients developed fever associated with neutropenia. There was one early death: a patient who developed a perforated abdominal viscus after her first course of therapy (no autopsy was performed). This patient was considered a nonresponder.

Three patients had cardiovascular problems after treatment. One patient with pericardial involvement of a tumor developed arrhythmias and signs of congestive heart failure while on therapy. After appropriate antiarrhythmic therapy, she completed treatment without sequelae. A second patient developed pericardial tamponade (cytology negative) and died of a pulmonary embolus 11 months after initiating therapy. The third patient was noted to have an ejection fraction of 50% after the first cycle of PAC and was removed from study and underwent radiation therapy. Approximately 18 months later, the patient developed constrictive pericarditis.

Another patient (a previous smoker) with local extension into the lung at diagnosis subsequently developed presumed radiation pneumonitis. No late episodes of congestive cardiomyopathy have been reported.

Response & Survival

Among 23 assessable patients, there were five CRs and 11 PRs to initial chemotherapy. Only one patient had

Table 2. Staging Classification for Thymoma

	Masaoka Staging ⁹	Gett Classification ¹⁵
Stage I	Macroscopically completely encapsulated and no microscopic capsular invasion	Encapsulated tumor, complete resection
Stage II	Macroscopic invasion into surrounding fatty tissue or mediastinal pleura Microscopic invasion into the capsule	Potential capsular invasion, complete resection
Stage III	Macroscopic invasion into neighboring organs (pericardium, great vessels, or lung)	Invasive tumor, complete resection
Stage IV	Pleural or pericardial dissemination of thymoma Lymphogeneous or hematogeneous metastases	Invasive tumor, biopsy Supraclavicular or distant pleural invasion Distant metastases

Table 3. Toxicity

Type	ECOG Grade (no. of patients)				
	1	2	3	4	5
Worst hematologic	5	6	3	11	—
Vomiting	4	6	4	—	—
Diarrhea	2	2	—	—	—
Infection	3	3	—	3	—
Cardiac	—	—	1	1	—
Mucositis	5	—	—	—	—
Neurologic/clinical	5	—	1	—	—
Genitourinary	6	1	—	—	—
Hepatic	5	—	—	—	—
Other	10	4	1	0	1*
Worst nonhematologic	6	11	6	2	1*

*One patient died of GI perforation after the second cycle of therapy. The patient also had grade 4 infection with sepsis and pneumonia.

progression of disease. Thus, the overall objective response rate (CR + PR) was 16 of 23 patients (69.6%; 95% confidence interval [CI] 47.1% to 86.8%).

One of the eleven patients exhibiting partial response was converted to a complete response after radiation therapy. Four of five patients with stable or minimal response improved to a complete (n = 1) or partial response (n = 3). No patient progressed during radiation therapy.

Of the 16 patients responsive to chemotherapy, eight have had relapses thus far. No obvious statistical differences were noted with respect to response rate and the number of scheduled cycles before radiation therapy (two v four), histology, sex, race, age, or performance status. It should be noted, however, that the numbers were too small for us to make meaningful conclusions. One of the two patients with thymic carcinoma responded to treatment. None of the five patients with a CR has had a relapse compared with eight of 11 (including two with second cancers) with partial responses. Of eight responding patients who subsequently developed recurrent disease, six had local recurrences with or without distant metastases. Three had distant metastases alone as the first sign of recurrence. All six assessable SECSG/SWOG-group patients had a relapse or tumor progression, whereas only seven of 17 ECOG patients (41.2%) have had relapses thus far. Only one of the six patients with stable disease remains progression free.

All relapses of thymoma or thymic carcinoma with objective responses occurred within 2 years of entry into the study. The median time to treatment failure was 93.2 months (range, 1 to 110 months; Fig 1). Using Kaplan-Meier estimates, the 5-year failure-free survival was 54.3% (SE, 10.8%).

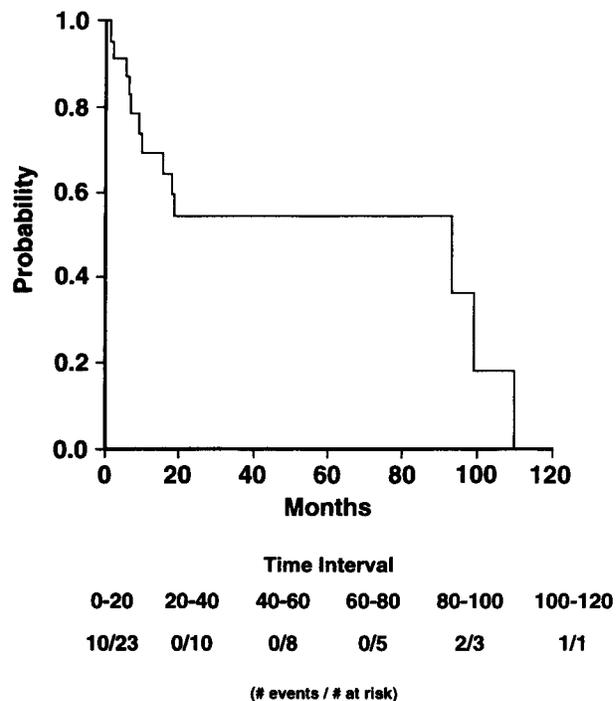


Fig 1. Time to treatment failure by Kaplan-Meier estimates. The time to treatment failure ranged from 1 month to almost 110 months, with a median of 93.2 months (95% CI, 9.6 to 99.2). The 5-year failure-free survival rate was 54.3% ± 10.8%.

The overall survival is shown in Fig 2. Eleven patients remain alive at the time of this report. The minimum follow-up is 14 months for ECOG patients and 125 months for the SECSG/SWOG patients. According to Kaplan-Meier estimates, the median survival time is 93 months (range, 1 to 110 months). The 5-year survival rate is calculated at 52.5% (SE, 12.1%). There has been one late recurrence of thymoma 8 years after entry into the study. Also of note, all of the six eligible patients entered onto the SECSG/SWOG have subsequently died. This compares with six deaths of 17 patients (35.3%) entered onto the ECOG portion. The median survival time for patients with stage III_a disease was 46.3 months (range, 20.3 months to infinity) and for stage III_b was 93.2 months (range, 30.4 to 110 months). The 5-year survival rate for stage III_a was undefined (because follow-up was not long enough) and for stage III_b was 65.7% (SE, 51.3% to 80.1%). The observed difference in survival rates between stages III_a and III_b was not statistically significant (log-rank test, *P* = .572). The exclusion of the two patients with thymic carcinoma from survival analysis did not alter the curves for overall or relapse-free survivals.

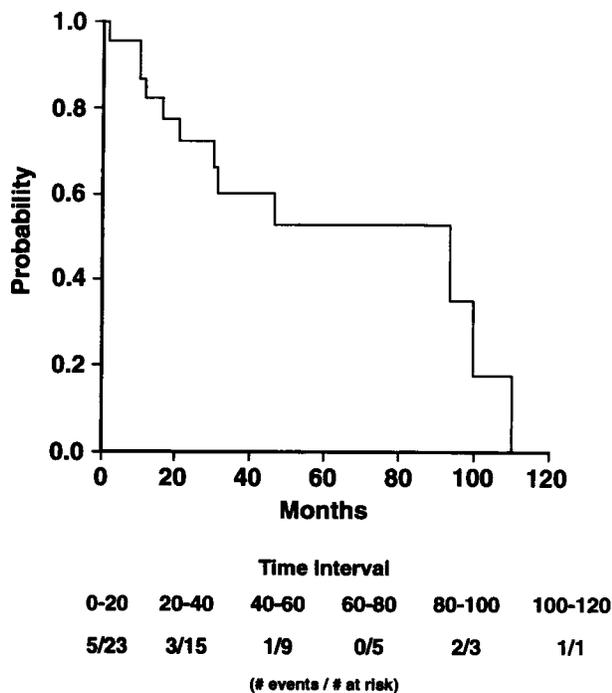


Fig 2. Overall survival by Kaplan-Meier estimates. Survival times ranged from 1 to 110 months with a median of 93 months (95% CI, 29.6 to 99.2 months). The 5-year survival rate was 52.5% ± 12.1%.

Other Illnesses

Several of the patients in this series were associated with concurrent illnesses suggestive of defective cellular immunity. These include three patients who developed unusual infections such as cryptococcal pneumonia, Listeria-associated meningitis, and disseminated herpes zoster infection. Five of the seven patients with myasthenia gravis showed an objective response to PAC chemotherapy compared with nine of 16 patients without a history of myasthenia gravis.

Four patients also developed second malignancies after entry onto the trial. This includes two patients with colon cancer, one of whom was also previously diagnosed with colon cancer 5 years before entry into the study. Two other patients developed large cell carcinoma of the lung (outside radiotherapy port) and adenocarcinoma of the esophagus 5 and 9 years, respectively, after entry into the study.

DISCUSSION

Primary therapy for thymoma is surgical. Fortunately, most patients can be successfully treated with such an approach. Up to one third of patients with thymoma,

however, will have locally invasive or unresectable disease for which additional therapy is warranted. The standard approach, radiation therapy, has had mixed success in such patients. Unfortunately, all published series addressing the role of radiation therapy for stage III thymoma have been the result of retrospective analysis. Monden et al¹⁰ reported six patients who underwent subtotal resection of thymoma. Five of the patients underwent radiation therapy and two underwent chemotherapy. Of these five patients who received radiation, only one patient survived. One patient died of an unrelated disease, and three additional patients with bulky unresectable disease, who underwent biopsy and were treated with involved field radiotherapy, also died as a result of their disease or chemotherapy (two of thymoma, one of chemotherapy complications).

Haniuda et al¹¹ reported a series of 70 patients who underwent complete resection and postoperative radiotherapy. Thirteen patients developed recurrent disease, including pleural metastases and distant disease (six had local recurrences alone with other metastasis). Haniuda et al concluded that in patients with completely resected stage II (with microscopic invasion of mediastinal structures) and stage III disease (macroscopic invasion of surrounding tissue such as lung, pericardium, SVC, and aorta), mediastinal radiotherapy was not sufficient in preventing pleural-based metastases. Nine of 22 patients (41%) with mediastinal pleural involvement developed pleural or distant metastases, and five of 18 patients (28%) with stage III disease developed recurrence.

Pollack et al¹² reported a series of 36 patients with thymoma treated at M. D. Anderson Cancer Center between 1962 and 1987. Of 15 patients who had gross residual disease after biopsy or subtotal resection of thymoma, 11 had relapses (including six after radiotherapy). The median time to relapse was 5 and 7 months after biopsy and subtotal resection, respectively. All but three of the 11 patients died after documentation of local recurrences. Similar results have been reported by other investigators.^{13,14}

Mornex et al¹⁵ reported on their experience of 90 patients with invasive thymoma treated at 10 cancer centers in France. Of the 58 patients with stage III disease (Gett Classification; Table 2) treated with radiation, 37 had prior biopsy only (III_b) and 21 had partial resection (III_a). Thirty-six of these 58 patients also had chemotherapy (not defined, but predominantly cisplatin-based) after surgery or before or after radiotherapy. None received concurrent chemotherapy with radiation. The 5- and 10-year survival rates calculated from the date of original surgery

were 64% and 43% for patients with stage III_a (partial resection) and 39% and 31% for patients with stage III_b (biopsy only), respectively. In this series, failure locally occurred in 14% of patients with III_a disease and in 41% of patients with III_b disease ($P = .055$). No clear differences in radiation dosage were noted between local failure and local controlled patients. In a review of the literature, the authors found that in 149 patients with stage I-IV thymoma, a significant difference in survival was noted between those who underwent complete resection, partial resection, and biopsy only (80% v 64% v 39%, respectively).

Curran et al¹³ reported one of the largest series of patients with stage III disease consisting of 117 patients with the diagnosis of thymoma treated at three institutions from 1960 to 1985, in which 28 patients underwent either biopsy ($n = 13$) or subtotal resection ($n = 15$) for stage III thymoma. Of 20 assessable patients who received postsurgical radiation therapy, there were nine recurrences, including four local and five distant metastases. One of the five patients with distant metastases also recurred in the mediastinum. In a review by Koh et al,¹⁶ 65% of 255 patients with incompletely resected thymoma had local control with radiation therapy; only 45% of 109 assessable patients survived 5 years (actuarial survival). These data include patients with minimal as well as gross residual disease.

Thus, it is logical to evaluate chemotherapy as a potential adjunct to local therapy, particularly for those patients with bulky disease. Several investigators have evaluated this approach. For example, Macchiarini et al¹⁷ treated seven patients with histologically confirmed stage III_a thymoma with three cycles of chemotherapy consisting of cisplatin, epirubicin, and etoposide every 3 weeks followed by surgery and postoperative radiotherapy. All seven patients had objective responses and are alive with a 2-year actuarial survival rate of 80%. Fornasiero et al¹⁸ treated 11 patients with invasive thymoma with the ADOC regimen, which consisted of cisplatin (50 mg/m²), doxorubicin (40 mg/m²), and cyclophosphamide (700 mg/m²) on day 4 and vincristine (0.6 mg/m²) on day 3. Courses were repeated every 3 weeks. Four complete and six partial responses were noted (overall response rate, 91%). The median survival time for all patients was 12.5 months, with only 5 of the 11 patients alive at the time of publication. Three patients received ADOC after primary radiotherapy, and all three patients have subsequently died. Eight patients received ADOC as first-line therapy, of whom five remained alive. In a previously reported⁴ intergroup trial, the PAC regimen produced a 50% objec-

tive response rate in 30 assessable patients with extensive thymoma or thymic carcinoma. Although this response rate for PAC makes it appear to be inferior to the ADOC regimen, the median survival time of 38 months with PAC (compared with 12.5 months for ADOC) brings the importance of vincristine into question.

This current trial has several limitations. First is the variability of the number of cycles of chemotherapy administered before radiation therapy (initially two cycles and later four cycles). If chemotherapy adversely impacted the survival of patients by delaying definitive radiotherapy, one would suspect an improved outcome for the patients entered on the earlier phase of the trial (with only two cycles of PAC before radiotherapy). This was not observed. Although follow-up is longer for the ECOG-directed effort, all six of the patients who received two cycles of PAC (SECSG/SWOG) have died compared with only 35% (six of 17 patients) treated with the four cycles of PAC (ECOG). This approach confirmed the sensitivity of thymoma to cisplatin-based combination therapy and provides a basis of comparison for future combined-modality trials in this disease setting.

Second, this trial does not prove that the addition of combination chemotherapy to radiation therapy improves the outcome of patients with limited unresectable thymoma. The 95% confidence intervals of the various series using radiation as monotherapy clearly overlap with those in this trial. However, this trial does confirm that PAC combination chemotherapy will produce objective responses in the majority of patients with limited disease. In select cases, primary reduction in the tumor size may allow smaller treatment fields for radiotherapy (potentially minimizing toxicity). The durability of these responses, particularly in patients with complete remission, is noteworthy. However, late recurrences with thymoma are not infrequent.

The third concern is a potential long-term deleterious impact of anthracycline therapy and radiation therapy. Three patients in this series developed cardiovascular complications. One patient had a decreased ejection fraction after being administered 50 mg/m² of doxorubicin. Two other patients developed pericardial problems (pericardial effusion with tamponade and constrictive pericarditis, respectively). There are known side effects of radiation therapy alone. Four cases of secondary malignancies were noted in this series. This association with thymoma has been previously described. Of these, only one case of adenocarcinoma of the esophagus might be attributable to therapy. This was in the same patient noted above who only received one course of PAC (be-

cause of decreased ejection fraction) before receiving definitive radiotherapy.

This report is one of the largest prospective trials conducted to date on patients with limited unresectable thymoma and confirms that thymoma is sensitive to combination chemotherapy. Durable remissions are observed with combined modality therapy, with a median duration of response of more than 8 years and a median survival time of more than 7 years. This trial also poses several ques-

tions. Is chemotherapy plus radiation therapy superior to radiation therapy alone? What is the optimal scheduling of radiation and chemotherapy? Should alternative regimens (eg, cisplatin, etoposide or cisplatin, ifosfamide, and etoposide) be used to minimize potential deleterious complications with radiation? Can more specific prognostic factors be defined to delineate good- and poor-risk populations? Trials addressing these and other issues should be encouraged but will require intergroup participation.

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