Chemotherapy for Advanced Thymoma

Preliminary Results of an Intergroup Study

Patrick J. Loehrer, Sr., MD; Carlos A. Perez, MD; Lawrence M. Roth, MD; F. Anthony Greco, MD; Robert B. Livingston, MD; and Lawrence H. Einhorn, MD

Objective: To determine the efficacy of combination therapy with cisplatin, doxorubicin, and cyclophosphamide alone or with radiotherapy for patients with extensive and those with limited unresectable thymoma.

Design: Nonrandomized, prospective phase I-II trial.

Setting: A Cooperative Oncology Group trial involving tertiary medical centers.

Patients: Twenty of twenty-two patients with measurable, extensive or limited, unresectable thymoma were evaluable for response.

Intervention: Patients were given cisplatin, 50 mg/m^2 body surface area, doxorubicin, 50 mg/m^2, and cyclophosphamide, 500 mg/m^2, on day 1, with cycles repeated every 21 days until progression or until the maximally tolerated total doxorubicin dosage (for example, 450 mg/m^2) was reached. Intravenous hydration with normal saline was administered during treatment courses. For responding patients with limited disease, 4500 cGy was administered to primary tumors after the second cycle of chemotherapy and before the initiation of the third cycle.

Measurements and Main Results: Three complete and eleven partial remissions were seen in 20 evaluable patients, for a total response rate of 70% (95% CI, 46% to 88%). The median duration of remission was 13 months with three patients remaining continuously disease free for over 2 years. The median survival time of all eligible patients was 59 months (CI, 22 months to infinity). Four patients developed infections, including listerial and aseptic meningitides, mucocutaneous candidiasis, and cryptococcal pneumonia, that were indicative of a defect in cell-mediated immunity.

Conclusions: Combination therapy with cisplatin, doxorubicin, and cyclophosphamide frequently produces objective remissions in patients with advanced thymoma. Further experience with this treatment regimen is warranted to clarify potential prognostic factors in patients with unresectable thymoma.

Annals of Internal Medicine. 1990;113:520-524.

From the Indiana University Hospital, Indianapolis, Indiana; the Mallinckrodt Institute of Radiology, St. Louis, Missouri; Vanderbilt University, Nashville, Tennessee; and the University of Washington, Seattle, Washington. For current author addresses, see end of text.

Thymomas are unusual neoplasms of the anterior mediastinum generally presenting in patients who are between 40 and 60 years of age (1). Although the association between thymoma and a myriad of medical conditions, such as myasthenia gravis, pure red cell aplasia, and hypogammaglobulinemia, has fascinated physicians for many years (2-4), little attention has been given to the systemic treatment of this disease. Fortunately, most patients with thymoma present with an encapsulated or noninvasive tumor that can be surgically resected for cure (1, 5, 6). Approximately one third of patients, however, have locally invasive or metastatic disease that may require adjunctive therapy with radiotherapy, chemotherapy, or both (1).

Several investigators have reported activity with various agents, such as cisplatin, doxorubicin, and cyclophosphamide, in patients with advanced thymoma, yet a prospective trial evaluating a specific chemotherapy regimen has not been reported. The combination of cisplatin, doxorubicin, and cyclophosphamide has been successfully used to treat ovarian and non-small-cell lung cancer. The rationale for administering chemotherapy before radiotherapy for patients with limited disease was to minimize the treatment field and assess the response rate to chemotherapy alone, before initiating "definitive radiotherapy." We report the interim results from an intergroup trial (involving the Southeastern Cancer Study Group and the Southwest Oncology Group) evaluating combination therapy with cisplatin, doxorubicin, and cyclophosphamide (PAC) in patients with advanced thymoma.

Methods

Patient Characteristics

From April 1983 through March 1988, 22 patients with locally unresectable or metastatic thymoma entered our trial. The patients' median age was 48 years (range, 28 to 68 years). The median Karnofsky performance status was 90 (range, 60 to 100). The minimal follow-up of patients was over 19 months, with a median of 41 months (range, 2 to more than 61 months). Twenty patients were eligible and fully evaluable for response and survival. Two patients were deemed to be ineligible after histologic review showed squamous cell carcinoma of the lung and thymic carcinoma, respectively. Most patients were classified as having mixed epithelial-lymphocytic tumors with 3 patients having pure epithelial thymoma. Of note, 6 patients had received their original diagnosis of thymoma 4 or more years before entering the study. Eight patients had previously received radiotherapy. Six patients had limited disease (defined below), and 14 patients had extensive disease, with the major sites of metastases being the pleura (7 patients) and the lungs (7 patients), but also including the liver, lymph nodes, and

brain. Only 1 patient had pre-existing symptoms from myasthenia gravis.

Eligibility Criteria

Eligible patients had histologically confirmed invasive, recurrent, or metastatic thymoma. Slides and blocks were sent for central pathology review. Eligible patients had a Karnofsky performance status of 50 or more and at least one bidimensionally measurable lesion. All eligible patients also had adequate renal function (serum creatinine level ≤ 133 μmol/L or creatinine clearance ≥ 1.17 mL/s), hepatic function (serum bilirubin level ≤ 36 μmol/L), and normal bone marrow reserve (leukocyte count $> 4.0 \times 10^9$/L and platelet count $\geq 125 \times 10^9$/L). In addition, eligible patients had not received chemotherapy with any of the study drugs (cisplatin, doxorubicin, or cyclophosphamide). Patients with a previous history of congestive heart failure, other malignancies within the previous 5 years (except for nonmelanomatous skin cancer, or cancer of the cervix [stage 0-IIA]) were ineligible.

Pretreatment studies included a history and physical examination, chest roentgenogram, complete blood count, serum chemistry panel, serum electrolytes, and creatinine. An electrocardiogram, ejection fraction, or both were done as indicated for patients with a previous history of ischemic heart disease or congestive heart failure. Computed tomography of the chest was done as indicated for tumor measurements. During treatment, history, and physical examination, serum chemistry panel and chest roentgenograms with or without computed tomography (as indicated) were done every 3 weeks to evaluate response and toxicity. All patients signed an informed written consent.

Treatment Regimen

Patients were classified as having "limited" disease if disease was confined to the mediastinum and ipsilateral superclavicular lymph node and all disease could be easily encompassed in a radiotherapy portal. "Extensive" disease was defined as that in which distant disease, including pleural or pulmonary metastases or both with or without mediastinal disease, was shown. Patients with surgically unresectable "limited" disease that progressed locally despite previous radiotherapy were also classified as having extensive disease.

The treatment regimen consisted of cisplatin, 50 mg/m^2 body surface area, in 250 mL of normal saline administered over 1 hour (schema in Figure 1). Doxorubicin, 50 mg/m^2, and cyclophosphamide, 500 mg/m^2, were both given by slow intravenous push. The use of concurrent corticosteroids, except for in treating myasthenia gravis, was specifically discouraged. All patients received pretreatment hydration with at least 1 L of 0.9% normal saline over at least 2 hours before and after chemotherapy with cisplatin. Patients received these chemotherapy treatments every 3 weeks for a maximum of nine cycles (the total cumulative doxorubicin dosage was 450 mg/m^2).

All patients were evaluated for response after two cycles of therapy. Patients with extensive disease whose conditions responded (those whose conditions were stable or in partial remission) were treated without interruption. For patients with limited disease whose conditions responded, split-course radiotherapy was administered before resumption of chemotherapy. After completion of chemotherapy, patients were followed every 6 to 8 weeks until relapse or death.

Radiotherapy

After treatment with two courses of induction chemotherapy, those patients with limited disease whose tumor measurements were stable or showed a partial response to induction chemotherapy received 4500 cGy to the primary tumor and the hilar and mediastinal lymph nodes in a split course consisting of 3000 cGy in ten fractions during weeks 7 and 8 with an additional 1500 cGy in five fractions administered to the residual tumor or the site of previous gross tumor during week 12 using a reduced port. For these patients, chemotherapy was withheld from weeks 7 to 12 and resumed within 4 weeks of completion of radiotherapy for an additional seven scheduled treatments. Irradiation was delivered with megavoltage photons (minimal treatment distance, 80 cm). The volume irradiated encompassed all radiographically evident tumors with a maximum of a 3-cm margin and the hilar and mediastinal lymph nodes with a 2-cm margin. Anterior-posterior and posterior-anterior portals were used to deliver a portion of the dose, so that the spinal cord would not receive doses higher than 3000 cGy. The remainder of the dose was delivered with oblique fields. Dose fractionation was 300 cGy/d.

Response Criteria

Complete remission was defined as the complete disappearance of all objective evidence (clinical and radiographic) of disease for at least 1 month. A partial remission was defined as a decrease of 50% or more in the sum of the products or perpendicular diameters of measurable disease for at least 1 month. Survival duration was measured from the first day of treatment until the day of death or the last follow-up visit. Response duration was measured from the date of the first evidence of response until relapse or death. Survival curves were plotted by the technique of Kaplan and Meier (9). Median survival times were calculated using the Kaplan-Meier estimates, and the corresponding 95% confidence intervals (CIs) were calculated by the method of Brookmeyer and Crowley (10).

Results

Toxicity

Eleven patients had grade II or III gastrointestinal toxicity manifested by diarrhea (1), nausea, and vomiting (10). Hematologic toxicity was generally minimal. The median hemoglobin nadir was 98 g/L (range, 86 to 121 g/L) and the median platelet nadir was 203×10^9/L (range, 56 to 330×10^9/L). The median leukocyte nadir was 2.0×10^9/L (range, 0.9 to 6.3×10^9/L), and six patients developed granulocytopenic fevers. Two patients with normal leukocyte counts after completion of chemotherapy developed meningitis (listerial and aseptic, respectively). One patient had extensive mucocutaneous candidiasis at presentation. A fourth patient developed cryptococcal pneumonia after completion of chemotherapy, but while receiving prednisone. There were no drug-related mortalities.

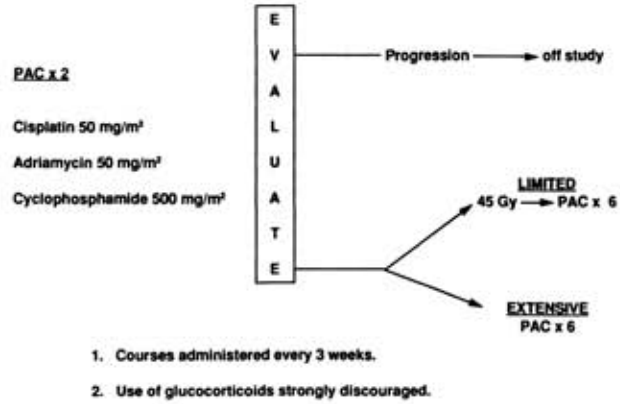

Figure 1. Schema of the protocol design for patients with limited and patients with extensive thymoma.

Response to Therapy

Three complete and eleven partial remissions were seen in this group, for an overall response rate of 70% (95% CI, 46% to 88%). Complete responses were seen in patients with mediastinal plus pleura, pleura only, and liver plus paraspinal disease, respectively. These responses occurred in 4 of 6 patients (66%; CI, 22% to 96%) with limited disease before initiation of radiotherapy and in 10 of 14 patients (71.4%; CI, 42% to 92%) with extensive disease. Although the protocol specified six additional cycles of chemotherapy after radiotherapy, only 2 of 5 responding patients with limited disease received two and three cycles of additional chemotherapy, respectively; 2 patients received only one additional cycle and 1 patient refused further therapy. Of note, 3 of the 6 patients who were originally diagnosed with thymoma 4 or more years before study entry responded with two complete and one partial remission. Five of eight patients who had previously received radiotherapy responded to the induction regimen. The median duration of remission was 13 months with 2 patients remaining disease free for over 4 years and 1 patient for over 3 years.

At present, 11 patients in our study have died, 10 from progressive disease and 1 from a second malignancy (colon cancer). One patient with progressive disease was lost to follow-up. The median survival of all eligible patients was 59 months (CI, 22 months to infinity). Six patients are alive after 4 or more years and 3 additional patients are alive after 5 or more years from the time they were entered in the study.

Discussion

Thymomas are infrequent tumors of the anterior mediastinum. The initial diagnosis is usually heralded by local symptoms (for example, cough, chest pain, dyspnea, superior vena caval obstruction), an abnormal chest radiograph in an asymptomatic adult, or by association with various paraneoplastic syndromes. Whereas most patients who develop thymomas are managed well with complete surgical excision of tumor, approximately one third of newly diagnosed patients present with locally invasive disease; for these patients, the chance of developing recurrent disease is roughly 20% to 50%. Although extrathoracic metastases occur, the most frequent sites of metastasis are the pleura and pericardium (1).

Experience with systemic chemotherapy for patients with metastatic or advanced thymoma is limited, but many case reports suggest that thymoma is a chemosensitive tumor. Cisplatin (11-15), corticosteroids (16-19), doxorubicin (19), and maytansine (20, 21) have all been shown to elicit objective responses when used as single agents in patients with metastatic thymoma. Several investigators have documented complete remissions with single-agent cisplatin therapy; however, in a recent prospective trial conducted by the Eastern Cooperative Oncology Group (13), cisplatin produced only two partial remissions in 21 fully evaluable patients with advanced thymoma. In other reports, investigators have observed favorable responses for patients treated with combination regimens containing doxorubicin, cisplatin, or both (22-27). At the initiation of our study, PAC combination chemotherapy at these dosages was the standard treatment for another epithelial malignancy, ovarian cancer (28). These data support the use of PAC combination therapy in patients with thymoma.

Our study shows a high degree of activity for cisplatin-based combination chemotherapy in the treatment of locally advanced or metastatic thymoma. Three complete and eleven partial remissions were noted, with an overall response rate of 70% and a median survival of nearly 5 years. These results compare quite favorably with those of the previously mentioned Eastern Cooperative Oncology Group trial (13), which evaluated therapy with cisplatin alone in a comparable patient population during a similar time frame. These data as well as the observation that five patients were originally diagnosed with thymoma over 5 years before entering the study, however, suggest that the disease of some patients with unresectable thymoma may have an indolent course without treatment. This prolonged natural history of the disease has been recognized (1, 27) and makes the ultimate effect of our regimen on overall survival in this relatively small series uncertain at present.

The degree of antitumor activity of corticosteroids in thymoma is uncertain, as remissions have generally been seen in those patients with mixed or lymphocyte-predominant thymomas. In thymomas, the epithelial element is thought to be the malignant component with the associated lymphocytes being reactive in nature (29, 30). Despite a specific avoidance of corticosteroids, unusual infections were seen in four patients in our series without concurrent granulocytopenia. Two patients developed meningitides (listerial [1 patient], aseptic [1 patient]). A third patient had extensive mucocutaneous candidiasis on initial diagnosis. The final patient developed cryptococcal pneumonia although he was receiving concurrent corticosteroids at diagnosis. Pretreatment evaluation of immunologic competency was not done as part of this study.

The association of thymomas with hypogammaglobulinemia has been previously reported, yet the association of infections with defects in cell-mediated immunity is less well documented. The cases of two patients with thymoma who developed *Pneumocystis carinii* pneumonia have previously been reported, but these patients were receiving concurrent corticosteroids (31, 32). One of these patients also developed progressive multifocal leukoencephalopathy with isolation of the Cruetzfeldt-Jakob virus (32). Two additional patients have been reported to have presented with fever and anergy to skin testing (33, 34); these latter patients also presented with leukocytosis of predominantly T-cell origin which improved with treatment (34). We have also seen additional cases of disseminated herpes, mucocutaneous candidiasis, and aseptic meningitis, respectively, in three previously untreated patients with thymoma who were not included in this series. The association between thymomas and atypical infections needs to be clarified; its effect on the design of future trials remains uncertain.

Radiotherapy has remained the mainstay of treatment

for limited unresectable thymoma. From a group of 117 cases reported by Curran and colleagues (35), none of 42 patients with completely resected encapsulated thymomas had recurring disease. However, 17 of 57 patients (30%) with microscopic or macroscopic invasive thymoma developed recurrent or metastatic thymoma with postoperative radiotherapy, implying that radiotherapy does not eliminate the risk for local recurrence. Finally, among 20 patients in this series with locally unresectable disease who received radiotherapy with curative intent, 9 patients (45%) developed local or distant recurrence, thus underscoring the need to evaluate the role of systemic treatment in this disease.

Primary tumor regression noted in patients in our series permitted the use of smaller radiotherapy ports for those with limited disease using combined-modality treatment. This "neoadjuvant" therapeutic approach had been previously suggested by Arriagada and colleagues (36). Tumor size reduction by chemotherapy could potentially diminish the size of radiotherapy portals and minimize toxicity from radiation. Because few patients with limited disease were included in this series, evaluation of the long-term benefit of this combined approach must await results from further study. Because of outpatients' poor compliance with chemotherapy after radiotherapy, in our continuing trial, patients with "limited disease" will receive four cycles of chemotherapy followed by radiotherapy alone to areas of residual disease. Conventional radiotherapy instead of split-course radiotherapy will be used in this ongoing study; our previous design was based on our experience with combined-modality treatment in patients with limited small-cell lung cancer (37).

In summary, our multi-institutional prospective trial showed clear activity of PAC combination chemotherapy in patients with advanced thymoma. The high response rate and long median survival of patients treated with PAC combination chemotherapy in our series compares favorably with historical data. Nonetheless, the disparity between the relapse-free survival and overall survival curves casts some doubt on the curative potential of this regimen. A broadened clinical expense with extended follow-up will be necessary to determine this potential. As such, this trial is continuing to accrue patients under the auspices of the Eastern Cooperative Oncology Group.

Acknowledgments: The authors thank Mrs. Debbi Jackson for manuscript preparation.

Grant Support: In part by National Cancer Institute Grants 50-829-48 and CA 39844-03.

Requests for Reprints: Patrick J. Loehrer, Sr., MD, Indiana University Hospital, Room A-109, 926 West Michigan Street, Indianapolis, IN 46202-5265.

Current Author Addresses: Drs. Loehrer, Roth, and Einhorn: Departments of Medicine and Pathology, Indiana University School of Medicine, 926 West Michigan Street, Indianapolis, IN 46202-5265.
Dr. Perez: Department of Radiation Therapy, Mallinckrodt Institute of Radiology, 5105 Kings Highway, St. Louis, MO 63110.
Dr. Greco: Vanderbilt University, Medical Center North A-2127, Nashville, TN 37232.
Dr. Livingston: Department of Oncology, University of Washington, 1959 North East Pacific Street, Seattle, WA 98195.

References

1. **Rosenberg JC.** Neoplasms of the mediastinum. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. 3d ed. Philadelphia: Lippincott; 1989:706-24.
2. **Robin M, Stravs B, Allen L.** Clinical disorders associated with thymic tumors. *Arch Intern Med*. 1964;**114**:389-98.
3. **Zeck JV, Todd EP, Dillon M, DeSimone P, Utley JR.** The role of thymectomy in red cell aplasia. *Ann Thorac Surg*. 1979;**28**:257-60.
4. **Batata MA, Martini N, Huvos AG, Aguilar RI, Beattie EJ Jr.** Thymomas: clinicopathologic features, therapy, and prognosis. *Cancer*. 1974;**34**:389-96.
5. **Verley JM, Hollmann KH.** Thymoma: a comparative study of clinical stages, histologic features, and survival in 200 cases. *Cancer*. 1985;**55**:1074-86.
6. **Wilkins E Jr, Castleman B.** Thymoma: a continuing survey at the Massachusetts General Hospital. *Ann Thorac Surg*. 1979;**28**:252-6.
7. **Norstrom DG, Tewfik HH, Latourette HB.** Thymoma: therapy and prognosis as related to operative staging. *Int J Radiat Oncol Biol Phys*. 1979;**5**:2059-62.
8. **Cohn LH, Grimes OF.** Surgical management of thymic neoplasms. *Surg Gynecol Obstet*. 1970;**131**:206-15.
9. **Kaplan E, Meier P.** Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;**53**:457-81.
10. **Brookmeyer R, Crowley J.** A confidence interval for the median survival time. *Biometrics*. 1982;**38**:29-41.
11. **Needles B, Kemeny N, Urmacher C.** Malignant thymoma: renal metastasis responding to cis-platinum. *Cancer*. 1981;**48**:223-6.
12. **Talley RW, O'Bryan RM, Gutterman JU, Brownlee RW, McCredie KB.** Clinical evaluation of toxic effects of cis-diamminedichloroplatinum (NSC 119875)—phase I clinical study. *Cancer Chemother Rep*. 1973;**57**:465-71.
13. **Bonomi P, Aisner S, Ettinger D, Finkelstein D.** Phase II trial of cisplatin recurrence in metastatic malignant thymoma: an ECOG trial [Abstract]. *Proc Am Soc Clin Oncol*. 1988;**7**:221.
14. **Cocconi G, Boni C, Cuomo A.** Long-lasting response to cis-platinum in recurrent malignant thymoma: case report. *Cancer*. 1982;**49**:1985-7.
15. **Levin L, Sealy R, Barron J.** Syndrome of inappropriate antidiuretic hormone secretion following cis-dichlorodiammineplatinum II in a patient with malignant thymoma. *Cancer*. 1982;**50**:2279-82.
16. **Green JD, Forman WH.** Response of thymoma to steroids. *Chest*. 1974;**65**:114-6.
17. **Posner JB, Howieson J, Civitkovic E.** "Disappearing" spinal cord compression: oncolytic effect of glucosteroids (and other chemotherapeutic agents) on epidural metastases. *Ann Neurol*. 1977;**2**:409-13.
18. **Shellito J, Khandekar JD, McKeever WP, Vick NA.** Invasive thymoma responsive to oral corticosteroids. *Cancer Treat Rep*. 1978;**62**:1397-400.
19. **Boston B.** Chemotherapy of invasive thymoma. *Cancer*. 1976;**38**:49-52.
20. **Chahinian AP, Bhardwaj S, Meyer RJ, Jaffrey IS, Kirschner PA, Holland JE.** Treatment of invasive or metastatic thymoma: report of eleven cases. *Cancer*. 1981;**47**:1752-61.
21. **Jaffrey IS, Denefrio JM, Chahinian AP.** Response to maytansine in a patient with malignant thymoma [Letter]. *Cancer Treat Rep*. 1980;**64**:193-4.
22. **Loehrer PJ, Bonomi P, Goldman S, et al.** Remission of invasive thymoma due to chemotherapy. *Chest*. 1985;**87**:377-80.
23. **Kosmidis PA, Iliopoulos E, Penetea S.** Combination chemotherapy with cyclophosphamide, adriamycin, and vincristine in malignant thymoma and myasthenia gravis. *Cancer*. 1988;**61**:1736-40.
24. **Dy C, Calvo FA, Mindan JP, et al.** Undifferentiated epithelial-rich invasive malignant thymoma: complete response to cisplatin, vinblastine, and bleomycin therapy. *J Clin Oncol*. 1988;**6**:536-42.
25. **Klippstein TH, Mitrou PS, Kochendorfer KJ, Bergmann L.** High-dose adriamycin (ADM) and cis-platinum (DDP) in advanced soft-tissue sarcomas and invasive thymomas. A pilot study. *Cancer Chemother Pharmacol*. 1984;**13**:78-81.
26. **Campbell MG, Pollard R, Al-Sarraf M.** A complete response in metastatic malignant thymoma to cis-platinum, doxorubicin and cyclophosphamide: a case report. *Cancer*. 1981;**48**:1315-7.
27. **Godel N, Boning L, Fredrik A, Holzel D, Hartenstein R, Wilmanns W.** Chemotherapy of invasive thymoma: a retrospective study of 22 cases. *Cancer*. 1989;**63**:1493-500.
28. **Ehrlich CE, Einhorn LH, Williams SD, Morgan J.** Chemotherapy for stage III-IV epithelial ovarian cancer with cis-dichlorodiammineplatinum (II), adriamycin, and cyclophosphamide: a preliminary report. *Cancer Treat Rep*. 1979;**63**:281-8.
29. **Masaoka A, Nagaoka Y, Maeda M, Monden Y, Seike Y.** Study on the ratio of lymphocytes of epithelial cells in thymoma. *Cancer*. 1977;**40**:1222-8.
30. **Lauriola L, Maggiano N, Marino M, Carbone A, Piantelli M, Musiani P.** Human thymoma: immunologic characteristics of the lymphocytic component. *Cancer*. 1981;**48**:1992-5.
31. **Hu E, Levine J.** Chemotherapy of malignant thymoma: case report and review of the literature. *Cancer*. 1986;**57**:1101-4.
32. Case records of the Massachusetts General Hospital. Weekly clin-

icopathological exercises. Case 27-1987. A 53-year-old man with multiple pulmonary nodules, recurrent hemoptysis, heart murmur, and sudden death. *N Engl J Med*. 1987;**316**:35-42.
33. **Cocconi G, Boni C, Cuomo A.** Long-lasting response to cis-platinum in recurrent malignant thymoma: case report. *Cancer*. 1982;**49**: 1985-7.
34. **Shachor A, Radnay J, Bernheim J, et al.** Malignant thymoma with peripheral blood lymphocytosis. *Cancer*. 1988;**61**:1222-7.
35. **Curran WJ Jr, Kornstein MJ, Broks JJ, Turrisi AT 3d.** Invasive thymoma: the role of mediastinal irradiation following complete or incomplete surgical resection. *J Clin Oncol*. 1988;**6**:1722-7.
36. **Arriagada R, Bretel JJ, Caillaud JM, et al.** Invasive carcinoma of the thymus: a multicenter retrospective review of 56 cases. *Eur J Cancer Clin Oncol*. 1984;**20**:69-74.
37. **Perez CA, Einhorn L, Oldham RK, et al.** Randomized trial of radiotherapy to the thorax in limited small-cell carcinoma of the lung treated with multiagent chemotherapy and elective brain irradiation: a preliminary report. *J Clin Oncol*. 1984;**2**:1200-8.