Cisplatin and Etoposide Combination Chemotherapy for Locally Advanced or Metastatic Thymoma: A Phase II Study of the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group

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Background: **Thymomas are rare neoplasms of the mediastinum. The role of chemotherapy in advanced thymomas is not fully established.**

Patients and Methods: **In the European Organization for Research and Treatment of Cancer (EORTC) Lung Cancer Cooperative Group, 16 patients with recurrent or metastatic malignant thymoma were entered over 6 years onto a study of combination chemotherapy that consisted of cisplatin 60 mg/m^2 on day 1 and etoposide 120 mg/m^2 on days 1, 2, and 3, every 3 weeks.**

Results: **A median of six courses per patient was administered. Main side effects of treatment were leukopenia, nausea and vomiting, and alopecia. Five complete responses and four partial responses were obtained, with a median response duration of 3.4 years. The median progression-free survival and survival times were 2.2 years and 4.3 years, respectively, with a median follow-up duration of 7 years.**

Conclusion: **The combination of cisplatin and etoposide is highly effective and well tolerated in advanced thymoma. The investigation of this combination in a neoadjuvant setting in unresectable invasive thymoma is warranted.**

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THYMOMAS represent 17% of mediastinal enlargements and are defined as neoplasms that arise from the epithelial cell in the thymus gland. Thymomas are usually slow-growing tumors, with a higher incidence at approximately 50 years of age. In approximately 50% of cases, thymomas are associated with myasthenia gravis or other disorders of the immune system. The malignant behavior of thymomas is not based on histologic criteria but on macroscopic or microscopic signs of invasiveness. Approximately 70% of thymomas are well encapsulated and therefore considered benign. Most malignant thymomas are characterized by local tissue invasion, less frequently by pleural metastases, and only 1% of invasive thymomas involve extrathoracic sites.[1,2]

Surgery is the mainstay treatment for noninvasive thymomas, and less than 2% of patients with well-encapsulated malignancies will relapse.[3,4] Surgery is often not radical in invasive thymomas and relapse ensues in approximately 20% of cases. The 10-year survival rate of patients with benign thymomas is 75% to 80%, while it is only 35% to 50% for invasive cases.[5,6]

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Mediastinal irradiation is often given to patients with subtotal resections or patients with minimal residual disease after surgery. Long-term survivors have been reported in a limited number of series.[7,8]

The role of chemotherapy in invasive thymomas has been subject of interest in recent years. In addition to a number of case reports described in the late 1970s and 1980s, a few larger series of more homogenously treated patients have been reported more recently. It appears from these studies that chemotherapy is effective in invasive thymomas and that it may have some role not only in the treatment of far advanced disease, but also in the neoadjuvant setting. Cisplatin has some activity in advanced thymomas,[9] and combination chemotherapy that includes cisplatin has been successfully tested in single-institution studies[10] and multicenter cooperative studies.[11,12]

The European Organization for Research and Treatment of Cancer (EORTC) Lung Cancer Cooperative Group started a multicenter study in advanced or recurrent malignant thymoma with the combination of cisplatin and etoposide. This combination was selected for its well-known activity in other malignancies (eg, small-cell and non–small-cell lung cancer),[13,14] its tolerable side effects, its possible synergy,[15] and the activity reported in a small series of four thymoma patients, of whom one achieved a partial response, two a minor response and one a mixed response.[16]

PATIENTS AND METHODS

To be admitted to this study, patients had to have biopsy-proven metastatic or recurrent invasive thymoma that was considered incurable by excision and/or by irradiation. Thymomas were classified

into three histologic types, as follows: predominantly lymphocytic, predominantly epithelial, or mixed lymphoepithelial.[1] Presence of measurable disease was requested and lesions in previously irradiated areas were accepted if definite progression was documented. Moreover, patients must have had an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 3, and bone marrow reserve, renal, hepatic, and cardiac functions within normal limits. Patients previously treated by chemotherapy were eligible, except those who received cisplatin or etoposide. Patients being treated with corticosteroids were not allowed onto the study. Informed consent was obtained before treatment start, in accordance with local policy.

Chemotherapy consisted of cisplatin 60 mg/m^2 given on day 1 and etoposide 120 mg/m^2 on days 1, 2, and 3. Cisplatin was administered over 1 hour, during a program of forced hydration, and etoposide diluted in 500 mL sodium chloride 0.9% was given over at least 30 minutes. Cycles were repeated every 3 weeks. Treatment was delayed for a leukocyte count less than 4,000/μL or platelet count less than 100,000/μL. If a more than 2-week delay was necessary, a 25% dose reduction of both agents was to be performed. Dose reductions were also performed based on nadir counts; if the leukocyte nadir and/or thrombocyte nadir was 1,000 to 1,999/μL or 50,000 to 74,999/μL, respectively, the dose of both drugs was reduced to 75% in the next cycles; if the nadirs were less than 1,000/μL and/or less than 50,000/μL respectively, the dose of both drugs was reduced by 50% in the next cycles. If the creatinine concentration increased to greater than 1.5 mg/dL and remained elevated for more than 2 weeks after the scheduled time of the next cycle, the cisplatin dose was reduced by 50%.

Patients who tolerated the treatment and did not progress were recommended to receive up to a maximum of eight consecutive cycles. Before the start of chemotherapy, patients underwent a physical examination, ECG, and evaluation of tumor sites by thorax computed tomographic scan; other radiologic investigations were performed if necessary to best estimate tumor extension. Blood cell counts, and determination of levels of hemoglobin, blood urea nitrogen, serum creatinine and creatinine clearance, total protein, albumin, electrolytes, and liver enzymes, and urinalysis were performed before each cycle of chemotherapy. Weekly blood cell counts were performed. Tumor response was evaluated after the first two cycles and then after every two cycles of chemotherapy. Response and toxicity were assessed according to World Health Organization criteria.[17] Duration of response was determined from registration to progression of disease. Duration of survival was determined from registration to death or last follow-up evaluation. Survival curves were estimated using the Kaplan-Meier technique.[18]

RESULTS

From September 1985 to August 1991, 16 patients were enrolled onto this phase II study from seven European institutions. The main patient characteristics are listed in Table 1. Most patients had undergone subtotal surgery, and none had received prior chemotherapy. One fourth of patients had myasthenia gravis at the start of treatment. Tumor characteristics are listed in Table 2. Tumor extension in all cases corresponded to either stage III (macroscopic invasion of neighboring organs, ie, pericardium, great vessels, and lung) or stage IV (pleural or pericardial seeding, or distant metastases), according to the classification of Masaoka et al.[19] Three patients had distant metastases in extrathoracic sites and two additional patients had tumor involvement of lung parenchyma.

Table 1. Patient Characteristics

No. of patients	16
Age, years	
Median	45
Range	20-67
Sex (male/female)	10/6
ECOG performance status	
0	7
1	5
2	4
Weight loss in last 3 months (%)	
≤ 5	10
> 5	5
Unknown	1
Myasthenia gravis at diagnosis	4
Prior sugery	
Radical	1
Subtotal	10
Biopsy only	5
Prior radiotherapy	4

A total of 94 cycles of chemotherapy were administered, with a median of six cycles per patient (range, two to nine). Chemotherapy toxicities are listed in Table 3. One patient received nine cycles after having achieved a partial remission, to fill in the gap before local irradiation could be given as consolidation. Nausea and vomiting, alopecia, and leukopenia were the most frequent toxicities. Antiemetic treatment mainly consisted of moderate doses of metoclopramide and none of the patients on study received anti 5-HT3 antiemetics. Dose reduction of

Table 2. Tumor Characteristics

Variable	No.
Tumor subtype	
Predominantly epithelial	7
Predominantly lymphocytic	4
Mixed lymphoepithelial	5
Extent of disease	
Mediastinal	6
Extramediastinal intrathoracic	7
Extrathoracic	3
Sites of disease	
Mediastinum	12
Pleura	8
Lung	2
Pericardium	1
Supraclavicular and axillary adenopathy	1
Abdominal paravertebral mass	1
Abdominal wall	1
Bone	1

Table 3. Toxicity

Toxicity	Total % of Patients	% with Grade 3-4
Leukopenia	100	51
Thrombocytopenia	13	
Anemia	31	
Nausea and vomiting	100	81
Alopecia	94	69
Diarrhea	35	6
Mucositis	19	6
Peripheral neuropathy	19	
Infection	19	6
Phlebitis	32	

both drugs was necessary in two patients due to severe hematologic toxicity. The most prominent toxicity was leukopenia; the median nadir value for leukocytes was 1.9×10^9/L (range, 0.6 to 3.8), and for platelets it was 140×10^9/L (range, 69 to 335). Treatment delays were recorded in 12 patients, with a median of 7 days (range, 2 to 14), and were due to hematologic toxicity in 11 patients and fever in one.

Major characteristics of each patient, together with the treatment outcome, are listed in Table 4. Response was assessable in all patients except one who died of cardiac arrest 4 weeks after the first cycle and could not be evaluated. This patient had a past history of heart infarction. Five patients achieved a complete remission, four a partial remission, six no change, and none progressed while on treatment. The response rate for 16 patients was therefore 56% (95% confidence interval, 30% to 80%). The overall response rate was 60% (95% confidence interval, 32% to 84%) if only the 15 patients assessable for response are considered. One patient who achieved a partial response after six cycles of chemotherapy underwent surgical debulking and postoperative irradiation.

Of nine responders, six have progressed thus far, and the median response duration was 3.4 years (range, 4 to 78+ months). Interestingly, two patients who did not have signs of major tumor regression on chemotherapy never progressed after a continuous follow-up period of more than 8 and 9 years (Table 4, patients no. 4 and 7). All major sites of disease responded in the 15 patients in whom response could be evaluated; in particular, six of 12 measurable mediastinal lesions and four of eight measurable pleural lesions regressed after chemotherapy.

Three of four patients with myasthenia gravis at treat-

Table 4. Major Patient Characteristics and Treatment Outcome

Patient No.	Age (years)/Sex	PS	MG	Surgery	RT	Histology	Disease Extent	Response	Response Duration	Survival Duration	Comments
1	46/F	2	No	Subtotal	No	LE	med pl	PR	1 yr, 10.5 mo	4 yr, 1 mo	Lung mets
2	34/M	0	Yes	Subtotal	No	L	med pl	CR	5 yr, 4 mo	9 yr, 1 mo*	On PD IFN → PD, DE → PR
3	20/M	0	No§	Subtotal	No	E	pl	CR	3 yr, 11 mo	6 yr, 5 mo	Bone mets
4	37/M	1	Yes	Subtotal	Yes	E	med	NC	9 yr, 2.5 mo*	9 yr, 2.5 mo*	MG improved, no PD
5	60/F	2	No	Subtotal	No	E	med	CR	6 yr, 6 mo*	6 yr, 6 mo*	
6	34/F	2	No	Biopsy	No	LE	med	PR	3 yr, 3 mo	7 yr, 11 mo*	6 cy PR → surg + RT; Lung met DE × 4 → PR; DE × 6 → PR
7	39/M	1	No	Subtotal	No	LE	med pl	NC	7 yr, 4 mo*	7 yr, 4 mo*	No PD
8	58/M	1	Yes	Biopsy	Yes	E	med pl abd	NA	1 mo	1 mo	CVA, no PD
9	46/F	1	No	Subtotal	No	L	pl per lung	PR	4 mo	2 yr, 2 mo	
10	55/M	1	No	Biopsy	No	LE	med	PR	1 yr, 11 mo	1 yr, 11 mo	Consolidation RT; pure RBC aplasia; no PD lost to follow-up
11	51/F	0	No	Biopsy	No	E	med	NC	1 yr, 10 mo*	6 yr*	
12	67/M	2	No	Subtotal	No	E	med lfn†	CR	5 yr, 2 mo*	5 yr, 2 mo*	
13	43/M	0	No	Biopsy	No	LE	med	NC	2 mo*	4 yr, 3 mo	
14	37/F	0	No	Radical	No	L	pl	NC	2 yr, 3 mo	2 yr, 3 mo	Pure RBC aplasia
15	37/M	0	Yes	Subtotal	Yes	L	lung	CR	1 yr, 1 mo	1 yr, 11 mo	Lung, bone mets
16	65/M	0	No	Subtotal	Yes	E	med pl bone abd‡	NC	1 yr	3 yr, 9.5 mo	

Abbreviations: F, female; M, male; PS, ECOG performance status; MG, myasthenia gravis; RT, radiotherapy; L, predominantly lymphocytic; E, predominantly epithelial; LE, mixed lymphoepithelial; med, mediastinum; pl, pleura; abd, abdomen; per, pericardium; lfn, lymph node; CR, complete response; PR, partial response; NC, no change; NA, not assessable; yr, years; mo, months; CVA, cardiovascular accident; mets, metastases; DE, cisplatin-etoposide; cy, cycles.

*No progression or still alive.

†Axillary and supraclavicular adenopathies.

‡Abdominal wall.

§Developed MG at progression of disease.

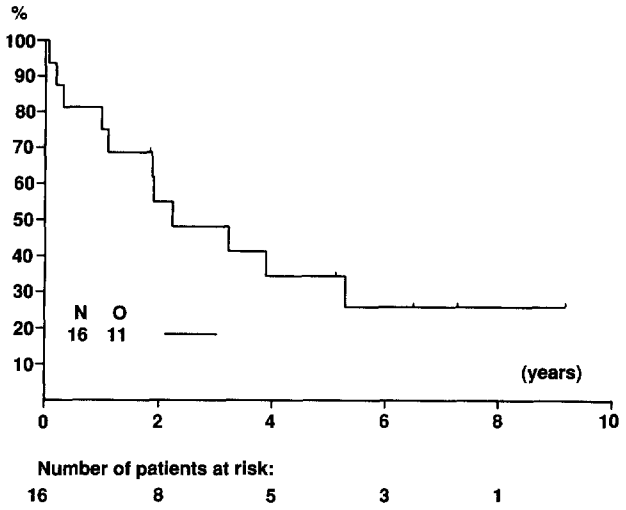

Fig 1. Progression-free survival.

ment start had significant neurologic improvement after chemotherapy, which was associated with tumor regression in two. In one of these patients (no. 4), no objective response was observed and signs of myasthenia gravis recurred despite no visible tumor progression. One patient developed myasthenia gravis after tumor progression and two others developed pure RBC aplasia.

Two patients who initially had a major response to cisplatin-etoposide were successfully rechallenged with the same chemotherapy and again obtained a major response (Table 4). In both patients, the off-chemotherapy interval was longer than 3 years.

The median follow-up time is 7 years and so far nine patients have been reported dead (66%). In six patients, disease progression was the cause of death, in one it was sudden cardiac arrest, and two died of severe infection after the diagnosis of pure RBC aplasia, probably due to coinvolvement of the WBC lineage. The median progression-free survival duration was 2.2 years, with 48%, 38%, and 26% of patients free of progression at 3, 5, and 7 years, respectively (Fig 1). The median survival time was 4.3 years; survival rates at 3, 5, and 7 years were 69%, 50%, and 42%, respectively. The overall survival curve is depicted in Fig 2.

DISCUSSION

The place of chemotherapy in the treatment of malignant thymoma is still uncertain because of the relative rarity of the disease.[2] Surgery remains the mainstay of treatment in both benign (noninvasive) and malignant (invasive) thymomas. When surgery can be radical, survival, even in case of invasive thymoma, is long-lasting. The 10-year survival rate for patients with noninvasive thymomas is approximately 80%,[5,6] and for invasive cases it is 35%.[5,6,20]

In our study, significant activity of the combination of cisplatin plus etoposide was observed in 16 patients with malignant thymomas enrolled onto a multicenter trial over a 5-year accrual period. The patients entered onto this study had good prognostic characteristics, and none had received prior chemotherapy. A response rate of 56% (60% if only strictly assessable patients are considered) was observed, of which 31% were complete, and the median response duration was 3.4 years, with a median survival time of 4.3 years. The toxicity in our study was rather tolerable, as most patients who responded to the chemotherapy program could continue on treatment for a median of six cycles. The median response duration and survival compare favorably with the results reported by the largest series published thus far.[10-12] The tumor load was limited in the majority of patients who underwent subtotal resection, as a result of a debulking procedure being used in most institutions for patients who clearly could not tolerate radical resection.[6] This may explain the long response durations and the long survival times reached in our series, which were assessed after a median follow-up period of 7 years. Interestingly, in two patients who did not have a major response to chemotherapy, no progression was observed after more than 7 and 9 years of observation. Although the tumor deposits still present and substantially unchanged after chemotherapy may represent sites of active disease, given the slow

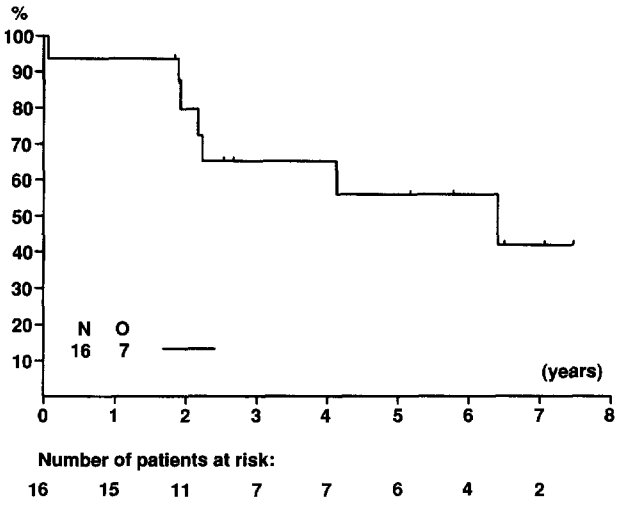

Fig 2. Overall survival.

growth rate of thymomas, this is unlikely, because chemotherapy was discontinued at completion of treatment in one patient and after four cycles in the other. Because neither patient underwent reexploration, it cannot be excluded that the disease sites were transformed into fibrotic rests as a reaction to chemotherapy, in analogy to what is frequently observed in highly responsive tumor types, such as testicular carcinomas.

Aggressive treatment of relapses is warranted in invasive thymoma; in a selected series of 21 patients with intrathoracic recurrences, surgery and irradiation or irradiation alone could produce a 70% 7-year survival rate.[21] Debulking surgery followed by radiotherapy is a well-recognized form of treatment in radically unresectable invasive thymoma.[6] Even in stage III and IV thymoma, when radically resected, the long-term survival rate is comparable to that of noninvasive thymomas: 80% at 5 years.[6] Also in patients in whom only a subtotal resection is possible, the survival rate is better than when only a biopsy is performed.[6,22] Thymomas are slow-growing tumors and long-term survival is often observed even in patients in whom first-line treatment (surgery) has failed to achieve cure.[5,23,24] The place of radiation therapy is less clear, and adjuvant radiotherapy is advocated in non-radically resected cases and in stage III and IV invasive thymoma.

The largest series ever published from a single institution (37 patients) was reported by Fornasiero et al.[10] The response rate was 92%, with 43% complete responses, and the median durations of responses and survival from the start of chemotherapy were 12 and 15 months, respectively. The combination chemotherapy of that study consisted of a four-drug regimen that included cisplatin, doxorubicin, vincristine, and cyclophosphamide. Our results also compare favorably with the United States intergroup study of cisplatin, doxorubicin, and cyclophosphamide (PAC) chemotherapy.[12] In that study, 30 eligible patients were accrued over 9 years, and the response rate was 50%, with three patients achieving complete remission (10%). The median response duration was 11.8 months. The median survival time was 37.7 months with a 3-year follow-up period, and the 5-year survival rate was 32%. The final report of this study[12] clearly demonstrated that long-term follow-up evaluation is necessary in this disease. In fact, an earlier analysis had reported a more exciting median survival time of nearly 5 years[11] in 20 eligible patients, monitored for a shorter period of time than in the final analysis.[12]

The role of chemotherapy in invasive thymoma was recently extensively reviewed by Tomiak and Evans.[25] Cisplatin-containing regimens appear to be the most active. However, in an ECOG study, cisplatin as a single agent only achieved two responses among 21 assessable patients.[9] In a review by Hu and Levine[26] in 1986, an overall response rate of 84% was observed with cisplatin-containing chemotherapy as compared with 58% with non–cisplatin-containing regimens. A prospective randomized trial to compare cisplatin-based chemotherapy versus no cisplatin has not been performed.

The presence of myasthenia gravis or other autoimmune diseases does not appear to influence response to chemotherapy. In two patients who responded to chemotherapy, myasthenic symptoms actually subsided. Similar findings have been described previously in several case reports.[27] Furthermore, chemotherapy given at relapse in some patients retains efficacy, especially if the off-treatment time is long. In our series, two patients were retreated with the same chemotherapy scheme and again achieved durable remissions. Some responses were also reported in the series by Fornasiero et al,[10] in which patients mainly received different combinations.

The prognosis of myasthenia gravis was poorer in patients with invasive than with noninvasive thymoma in a previous series,[22] but more recent series have shown that patients with myasthenia gravis actually appear to have a better prognosis than those without it, probably due to earlier diagnosis of thymoma in these patients,[20] as well as improved medical and anesthesiologic treatment of myasthenic patients who undergo surgery.

Histology in our study did not appear to have a clear influence on response to chemotherapy or survival. Conflicting findings have been reported in the literature concerning the impact of different histologic types[6,22] on survival. This has been further complicated by the development of additional histologic subclassifications.[28] Histologic diagnosis of thymoma remains difficult, and histology is advised to reach a definite diagnosis of thymoma. Probably the only differential diagnosis worth making is to distinguish thymomas (which are malignant on the basis of their behavior, ie, invasiveness and metastases) from thymic carcinomas (cytologically malignant). The latter tumor type appears to occur much more infrequently than thymomas, has a more aggressive behavior,[29] and is virtually never associated with paraneoplastic diseases.[30] Although reports are scanty, in a recent series of five cases, three responses were observed in patients treated with cisplatin-containing chemotherapy,[31] which indicates that there is also probably a significant chemosensitivity in this tumor type.

In our study, performance status, sex, and type of resection did not appear to have a great influence on response or survival, although the number of patients is relatively

small. However, in the intergroup trial, a worse performance status was more often associated with a lower response rate.[12]

Experience with neoadjuvant chemotherapy in grossly invasive thymomas is lacking. As reviewed by Tomiak and Evans[25] in 1993, 61 patients have received neoadjuvant chemotherapy followed by surgery in several small studies. The overall response rate was 89%. Of 22 patients who underwent surgery, 50% had complete pathologic resection. Interestingly, all had received cisplatin-based chemotherapy. Pathologically documented complete remissions have been identified. Also, in the study reported by Fornasiero et al,[10] seven of 16 complete remissions could be pathologically confirmed.

In the intergroup study EST 4589 recently reported, patients with untreated unresectable thymomas limited to the mediastinum received PAC chemotherapy plus radiotherapy. In 26 such patients enrolled over 10 years, there was a 62% response rate before radiotherapy, and the 5-year survival rate was 44.5%.[32] The 5-year survival rate reported in this neoadjuvant chemotherapy study is rather similar to the 50% 5-year survival rate in our study, in which almost 40% of patients (six of 16) had mediastinal disease only.

In conclusion, combination chemotherapy with cisplatin-etoposide is a well-tolerated and effective regimen in patients with recurrent of metastatic malignant thymoma. Tests of its use in a neoadjuvant setting are warranted. Given the rarity of the disease, this type of study will only be feasible in a multicenter cooperative setting.

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