Abstract. Aim: Thymoma is a rare neoplasm of the mediastinum, for which very few data on the efficacy and safety of chemotherapy and chemoradiotherapy are available. The objective of this pilot study was to assess the safety and efficacy of cisplatin, etoposide, and radiotherapy for thymoma. Patients and Methods: Patients with advanced, previously-untreated thymoma (Masaoka classification), measurable disease, and a performance status of 0-2 were eligible, and were treated with cisplatin-plus-etoposide, together with radiotherapy when possible. Results: One patient achieved complete response, and seven achieved partial responses. Progression-free survival was 37.7 months (95% confidence interval = 18.6-56.8 months). Ten patients had grade 4 neutropenia, and five patients had grade 3 febrile neutropenia. However, other toxicities were relatively mild. To date, only five patients (45.5%) have died, and the median survival time is 128.1 months (95% confidence interval = 51.6-204.6 months). Patients treated with chemoradiotherapy had a good response and long progression-free survival. Conclusion: The combination of cisplatin and etoposide with or without radiotherapy is effective for advanced thymoma, and has an acceptable toxicity.

Thymoma is a neoplasm of the thymus that originates in the gland’s epithelial tissue, with an annual incidence of 1.5 per million person years. Despite its rarity, it still represents the most common neoplasm of the anterior mediastinum (1, 2). Thymomas are typically slow-growing and spread by local extension in most cases, and two-thirds of patients are treated by surgical resection. Those who cannot undergo resection have usually been diagnosed with locally-advanced disease or distant metastases (3-5). Because tumor progression is slow, multimodality therapy with surgery, radiation, and chemotherapy can be indicated (6-10).

When this study started, there had only been a few clinical trials for this disease due to its rarity. The chemotherapy regimens used were cisplatin-plus-doxorubicin and cyclophosphamide, or cisplatin and etoposide, or cisplatin-plus-doxorubicin, vincristine and cyclophosphamide. However, these trials included only a small number of patients, some of whom actually had thymic cancer. More data are required on the safety and efficacy of chemotherapy and chemoradiotherapy for malignant thymoma. Given the potential benefits of multimodality therapy for this disease, our Institution initiated a prospective study of treatment-naïve patients with advanced thymoma using cisplatin and etoposide with or without radiotherapy. The primary endpoint of the trial was the objective response rate (ORR) and overall survival (OS), and the secondary end-points were progression-free survival (PFS), and safety.

Patients and Methods

Patients. Eligible patients were aged between 20 and 75 years, with histologically-confirmed invasive, recurrent, or metastatic thymoma that was not amenable to potentially curative surgery. In addition, the lesion had to be measurable in at least one dimension on radiographic imaging. All eligible patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2 and adequate bone marrow reserve (with a white cell count ≥4,000 cells/mm³, hemoglobin ≥9.5 mg/dl, and a platelet count of ≤100,000 cells/mm³), renal function (creatinine ≤1.2 mg/dl; blood urea nitrogen ≤25 mg/dl), hepatic function (serum bilirubin ≤1.5 mg/dl; transaminase ≤100 IU/l), and lung function (PaO₂ ≥70 Torr). Patients were not eligible if they had prior malignancies or if they were pregnant or lactating. This study followed the ethical principles of the Declaration of Helsinki, and the local Institution Review Board approved this protocol prior to initiation of the study (approval #379). All patients provided written informed consent before study-related procedures were performed.
**Treatment regimen.** Patients received etoposide at 100 mg/m² intravenously (i.v.) over 1 h followed by cisplatin i.v. over 90 min on day 1, and etoposide at 100 mg/m² i.v. over one hour on days 2 and 3. All patients received hydration, mainly by isotonic sodium chloride solution – at least 1,500 ml on day 1 and 1,000 ml on days 2 and 3. All patients were also administered prophylactic doses of antiemetic medications including steroid and 5-hydroxytryptamine-3 receptor antagonists. Treatments were repeated every 21 days for four courses, and were only stopped if the patients developed unacceptable toxicity or progressive disease (PD). Patients were evaluated using a chest computed tomographic (CT) scan. When the tumor was localized and radiotherapy was possible, we administered treatment with concurrent chemotherapy (cisplatin plus etoposide) and radiotherapy at 45 Gy in 30 fractions for the weeks (1.5-Gy b.i.d. fractionations). To be eligible for radiotherapy, the field had to be lower than the unilateral pulmonary half.

**Evaluation.** Pre-treatment evaluation included medical history and physical examination, complete blood count and metabolic profile, a CT scan of the chest and abdomen, and a pregnancy test (for women of child-bearing age). Evaluation during treatment included physical examination, assessment of toxicity, and a complete blood count and blood biochemistry before each cycle. The thymoma was assessed using a CT scan after the second and fourth cycles and upon disease progression.

**Design and statistical analysis.** This was a one-arm, single Institution, pilot study to evaluate the efficacy and safety of cisplatin, etoposide, and radiotherapy. The endpoints of the present study were ORR, PFS, OS, and toxicity.

Response was evaluated using the Response Evaluation Criteria in Solid Tumors version 1.0 (11), and adverse events were assessed using the Common Toxicity Criteria version 2.0 (12). PFS was defined as the time from enrollment to the date of confirmed PD or the date of death from any cause. OS was defined as the time from study registration until death from any cause. Patients not known to have died or to have suffered progression were censored at the date of the last progression-free assessment.

Kaplan–Meier plots were used for PFS and OS analysis, and the median and 95% confidence intervals (CIs) were determined. The incidence of adverse events was calculated for each course, and the distribution of the best overall responses was summarized in patients with target lesions. All eligible and treated patients were included in the response and survival analyses, and all treated patients were included in the toxicity analysis.

**Results**

Eleven patients were enrolled in the present study between November 1997 and September 2012, six of whom were men (Table I). The median patient age was 60 years (range=29-73 years). All patients had a PS of 0 or 1. Histologically, all patients had invasive thymoma, rather than thymic carcinoma. Masaoka stage III, IVa, and IVb disease was present in three, six, and two patients, respectively; six patients were able to receive concurrent radiotherapy.

The efficacy over the total treatment period is shown in Table II. The overall response rate was 72.7%, and there was one case of complete response (CR) and seven partial responses (PRs), with no cases of PD. All 11 patients were assessable for PFS and OS. With a median follow-up time of 62.0 months (range=6.2-123.9 months), five patients were still alive. The median PFS for all patients was 37.7 months (95% CI=18.6-56.8 months; Figure 1a), whereas the median OS was 128.1 months (95% CI=51.6-204.6 months; Figure 1b). Amongst the patients treated with concurrent radiotherapy, the ORR, PFS, and OS was 100%, 52.1 months, and 170.7 months, respectively, while amongst patients undergoing chemotherapy alone, ORR, PFS and OS was 40%, 31.4 months (p=0.155), and 40.8 months (p=0.254), respectively (Table II).

The major toxicities observed over the total treatment period are summarized in Table III. The most common adverse events were hematological abnormalities, including leukopenia and neutropenia. The hematological adverse events that were ≥grade 3-including leukopenia (90.9%), neutropenia (100%), and anemia (9.1%). There were three cases of grade 4 leukopenia and 10 cases of grade 4 neutropenia. However, there were no treatment-related deaths. The adverse events that occurred in this study were well-managed, and most of the patients recovered following dose adjustment or discontinuation of the study treatment. Non-hematological toxicities of grade 3 or more included febrile neutropenia (45.5%), and all other non-hematological toxicities were of grade 2 or less.

Six out of 11 patients (54.5%) received additional chemotherapy, and three received carboplatin and paclitaxel as second-line chemotherapy.

**Discussion**

In the present trial, cisplatin and etoposide treatment resulted in an ORR of 72.7% in patients with advanced thymoma with a median follow-up of 62.0 months (range=6.2-123.9 months). The median PFS and OS were 37.7 months (95% CI=18.6-
56.8 months) and 128.1 months (95% CI=51.6-204.6 months), respectively. This combination therapy demonstrated a promising response, particularly when combined with radiotherapy, and was well-tolerated.

Anthracycline-based regimens are the current standard-of-care for thymic malignancies according to the results of various phase II clinical trials, but they have not been tested in a phase III study. Fornasiero et al. reported their 13 years of experience treating 37 patients with stage III and IV thymoma who were administered cisplatin, doxorubicin, vincristine, and cyclophosphamide combination chemotherapy (6). The ORR was 91.8%, with 43% of patients achieving CR, but the median survival time was only 15 months. Loehrer et al. reported a 50% ORR with 10% of patients achieving a CR, and a median survival time of 37.7 months in an inter-group trial in which 29 patients with thymoma and 1 patient with thymic carcinoma with metastatic or locally progressive recurrent disease who were treated with paclitaxel (7). In another phase II study using a multi-disciplinary approach with induction chemotherapy followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable thymoma (10), 22 patients received induction chemotherapy with PAC plus prednisone for three cycles. The authors reported that induction chemotherapy resulted in a 14% CR and a 63% PR rate. However, anthracyclines are known to be associated with cardiomyopathy, especially when combined with radiotherapy. Therefore, non-anthracycline regimens may be preferable for patients treated with chemoradiation therapy.

The European Organization for Research and Treatment of Cancer conducted a study in which 16 patients with thymoma and 1 patient with thymic carcinoma with metastatic or locally progressive recurrent disease who were treated with paclitaxel (7). In another phase II study using a multi-disciplinary approach with induction chemotherapy followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable thymoma (10), 22 patients received induction chemotherapy with PAC plus prednisone for three cycles. The authors reported that induction chemotherapy resulted in a 14% CR and a 63% PR rate. However, anthracyclines are known to be associated with cardiomyopathy, especially when combined with radiotherapy. Therefore, non-anthracycline regimens may be preferable for patients treated with chemoradiation therapy.

Table II. Treatment efficacy (N=11).

<table>
<thead>
<tr>
<th>Response</th>
<th>All patients (N=11)</th>
<th>Chemotherapy + RT (N=6)</th>
<th>Chemotherapy-only (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>7</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Overall response rate, %</td>
<td>72.7</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>Disease control rate, %</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS (95% CI), months</td>
<td>37.7 (18.6-56.8)</td>
<td>52.1</td>
<td>31.4</td>
</tr>
<tr>
<td>OS (95% CI), months</td>
<td>128.1 (51.6-204.6)</td>
<td>170.7</td>
<td>40.8</td>
</tr>
</tbody>
</table>

CI: Confidence interval; RT: radiotherapy; PFS: progression-free survival; OS: overall survival.

Figure 1. Progression-free (A) and overall (B) survival curves for the patients in this study.
advanced or recurrent thymoma were treated with cisplatin and etoposide. In this trial, five patients achieved CR and four achieved PR (ORR, 56%) (13). On the basis of single-agent activity of ifosfamide in thymoma (14), 20 patients with advanced thymoma and eight patients with thymic carcinoma were treated with etoposide, ifosfamide, and cisplatin in an inter-group trial conducted by ECOG. An ORR of 35% and 25% was reported in patients with thymoma and thymic carcinoma, respectively. Grassin et al. reported similarly poor results (PR, 25%) in a study of 16 patients treated with etoposide, ifosfamide, and cisplatin (15). These cisplatin plus etoposide-based regimens produced apparently inferior response rates to those previously reported for anthracycline-based regimens (16). Furthermore, in the study reported here, the ORR of 40% for patients treated with chemotherapy-alone was similar to that found in previous studies. However, there was an ORR of 100% for patients treated with che...


12 Common Toxicity Criteria Manual, common toxicity criteria, version 2.0: June 1, 1999.


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