Combination Chemotherapy with Doxorubicin, Vincristine, Cyclophosphamide, and Platinum Compounds for Advanced Thymic Carcinoma

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Introduction: Thymic carcinoma is a rare epithelial neoplasm that tends to be aggressive and metastasize widely. The optimal chemotherapy for unresectable advanced thymic carcinoma has not yet been established because of its rare occurrence. The purpose of this study was to evaluate the efficacy and tolerability of combination chemotherapy with doxorubicin, vincristine, cyclophosphamide, and platinum compounds for advanced thymic carcinoma.

Methods: A retrospective analysis of 34 patients with untreated and unresectable thymic carcinoma who received chemotherapy with doxorubicin, vincristine, cyclophosphamide, and platinum compounds between 1996 and 2010 was conducted. Twenty-nine patients were treated with a combination of cisplatin (50 mg/m^2) and doxorubicin (40 mg/m^2) on day 1, vincristine (0.6 mg/m^2) on day 3, and cyclophosphamide (700 mg/m^2) on day 4. Five patients were treated with carboplatin (area under the curve of 3.0 minutes · mg/ml) instead of cisplatin.

Results: The responses of all 34 patients to the current regimen were assessed. The median number of treatment cycles for the present chemotherapy was 4. The overall response rate and disease control rate were 50.0% and 88.2%, respectively. The median survival was 21.3 months (95% confidence interval [CI], 15.0–37.2 months), and the 1-year and 3-year survival rates were 72.7% (95% CI, 56.8–88.6%) and 34.4% (95% CI, 16.2–52.6%), respectively. The most common adverse event was leukopenia/neutropenia, and nonhematological toxicities were mild.

Conclusions: Combination chemotherapy with doxorubicin, vincristine, cyclophosphamide, and platinum compounds is an effective and well-tolerated treatment for unresectable advanced thymic carcinoma.

Key Words: Thymic carcinoma, Chemotherapy, Platinum.

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Thymic carcinoma is a rare epithelial neoplasm with malignant cytologic features, and it accounts for approximately 5 to 36% of all thymic epithelial tumors.[1–3] The clinical course of thymic carcinoma tends to be much more aggressive than that of thymoma, and thymic carcinoma also tends to metastasize widely, which results in poor outcome.[2–7] Therefore, although systemic chemotherapy could play an important role in the treatment of thymic carcinoma, the optimal regimen has not been established because of the rare occurrence of this malignancy. There are few reports describing possible chemotherapy strategies for advanced thymic carcinoma, and these are based on small series and/or retrospective studies.[8–16] These reports have indicated that thymic carcinoma is relatively sensitive to chemotherapy, and cisplatin-based chemotherapies have shown promising results in certain patients with advanced thymic carcinoma. Yoh et al.[12] evaluated the efficacy of CODE (cisplatin, vincristine, doxorubicin, and etoposide) therapy in 12 patients with thymic carcinoma and reported a response rate (RR) of 41.7%. Igawa et al.[14] also reported the efficacy of carboplatin plus paclitaxel therapy in 11 patients with a RR of 36.4%.

Combination chemotherapy with cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC) was initially reported for the treatment of invasive thymoma. Fornasiero et al.[17] administered ADOC chemotherapy to 37 patients with unresectable invasive thymoma and reported a RR of 91.8% and a 43% complete remission. Meanwhile, Koizumi et al.[11] described eight cases with thymic carcinoma treated with ADOC chemotherapy and reported a RR of 75%. In addition, Kitami et al.[10] reported that all four cases who received modified ADOC (nedaplatin, doxorubicin, vincristine, and cyclophosphamide) chemotherapy obtained partial responses (PRs).

This study is a retrospective analysis of 34 patients with unresectable thymic carcinoma who received chemotherapy with doxorubicin, vincristine, cyclophosphamide, and platinum compounds in our hospital in the first-line setting. In this study, the efficacy and the tolerability of this combination chemotherapy for the treatment of advanced thymic carcinoma were assessed.

PATIENTS AND METHODS

A total of 38 consecutive patients with thymic carcinoma were admitted to the Respiratory Division of Shinshu

University hospital from August 1996 to March 2010. All patients were histologically diagnosed as thymic carcinoma based on the World Health Organization (WHO) criteria.[18] The histological samples were obtained by percutaneous computed tomography-guided biopsy, video-assisted thoracic surgery, or cervical lymph node biopsy. All patients had local invasion and/or distant metastasis at the time of presentation and were considered to have stage IVa or IVb disease according to Masaoka's classification.[19] Thirty-four of 38 patients were previously untreated and received systemic chemotherapy as the first-line treatment as described later. A physical examination, complete blood cell count, biochemistry examination, chest radiography, computed tomography scans of the thorax and abdomen, a bone scintigraphy or F-18 fluorodeoxyglucose positron emission tomography, and magnetic resonance imaging scan of the brain were performed for all patients as a pretreatment evaluation. Before the chemotherapy, written informed consent was obtained from all the subjects.

The combination chemotherapy with cisplatin (50 mg/m^2) and doxorubicin (40 mg/m^2) on day 1, vincristine (0.6 mg/m^2) on day 3, and cyclophosphamide (700 mg/m^2) on day 4, which is termed ADOC chemotherapy, was performed in 29 patients. Five patients were treated with carboplatin (area under the curve of 3.0 minutes · mg/ml) instead of cisplatin because of insufficient renal function, poor performance status (PS), or advanced age. All drugs were administered intravenously, and dexamethasone (8 mg) and/or granisetron (3 mg) were administered for the prevention of emesis induced by the chemotherapy. This regimen was repeated every 3 to 4 weeks and continued to the maximum of six cycles, if the tumor responded to the treatment and the toxicities were acceptable. Granulocyte colony stimulating factor was used as treatment for neutropenia but was not used routinely as a prophylactic treatment. Subsequent doses of the anticancer drugs were modified on the basis of hematological and nonhematological toxicities at the discretion of the physician in charge. If the patient's condition allowed it, second-line and further treatments after the current chemotherapy were also performed at the discretion of the attending physician.

The response to chemotherapy was evaluated using the WHO standard response criteria[20] in patients who were treated by 2002 and the RECIST[21] in patients from 2003 onward. The overall survival time was measured from the first day of the treatment with the current combination chemotherapy to the date of death or last follow-up. Fisher's exact test was applied to compare RRs between cisplatin and carboplatin groups. The survival curves were calculated using the Kaplan–Meier method[22] and compared among responses to the chemotherapy with the log-rank test. A p value of less than 0.05 was considered statistically significant. All statistical analyses were performed using MedCalc version 11.4.4 (MedCalc Software, Mariakerke, Belgium).

Toxicities associated with chemotherapy were graded according to the WHO criteria[23] in patients treated by 1999, the National Cancer Institute-Common Toxicity Criteria version 2.0[24] in patients from 2000 to 2004, and the Common Terminology Criteria for Adverse Events version 3.0[25] in patients from 2005 onward.

RESULTS

Patient Characteristics

The characteristics of 34 patients are listed in Table 1. Twenty-two patients were men, and 12 women, with median age of 56 years (range, 36–82 years). Twenty-eight patients (82.4%) had PS of 0 or 1 according to the Eastern Cooperative Oncology Group scale.[26] Histological subtypes of thymic carcinoma in the current patients were squamous cell carcinoma in 25 patients (73.5%), small cell carcinoma in two patients (5.9%), large cell neuroendocrine carcinoma in one patient (2.9%), and undifferentiated carcinoma in six patients (17.6%). The diagnoses of the three patients with small cell carcinoma or large cell neuroendocrine carcinoma were based on the radiographic and bronchoscopic findings with absence of intrapulmonary and lymph node lesions. Twelve patients (35.3%) had stage IVa disease, and 22 (64.7%) stage IVb disease, according to Masaoka's classification.[19]

Response to Chemotherapy and Survival

The median number of treatment cycles was 4 (range, 1–6 cycles, Table 1). The responses of the 34 patients to the current chemotherapy are listed in Table 2. PR was achieved in 17 patients, 13 patients showed stable disease (SD), and only four patients demonstrated progressive disease (PD). The overall RR and disease control rate (DCR) were 50.0% and 88.2%, respectively. Three patients were treated with radical surgical resection following the current treatment

TABLE 1. Patient Characteristics

Total number of patients	34
Gender	
Male	22
Female	12
Age (yr)	
Median	56
Range	36–82
Performance status (ECOG)	
0	23
1	5
2	6
Histological subtype	
Squamous cell carcinoma	25
Small cell carcinoma	2
LCNEC	1
Undifferentiated carcinoma	6
Clinical stage (Masaoka)	
IVa	12
IVb	22
Cycles of the current therapy delivered	
Median	4
Range	1–6

ECOG, Eastern Cooperative Oncology Group; LCNEC, large cell neuroendocrine carcinoma.

TABLE 2. Responses to Chemotherapy with Doxorubicin, Vincristine, Cyclophosphamide, and Platinum Compounds

	No. of Patients	Percentage
Complete response	0	0
Partial response	17	50.0
Stable disease	13	38.2
Progressive disease	4	11.8

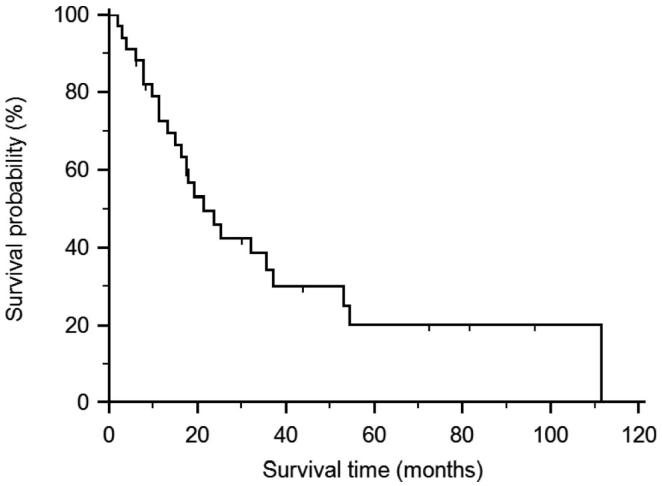

FIGURE 1. Overall survival curve for the 34 patients included in the study. The median survival time was 21.3 months.

regimen based on favorable tumor reduction in response to chemotherapy.

The median follow-up time was 35.5 months (range, 6.2–96.5 months). Figure 1 shows the overall survival curve for 34 patients. The median survival time (MST) was 21.3 months (95% confidence interval [CI], 15.0–37.2 months). The 1- and 3-year survival rates were estimated at 72.7% (95% CI, 56.8–88.6%) and 34.4% (95% CI, 16.2–52.6%), respectively. When the patients were grouped according to the responses to chemotherapy, the MSTs in patients who achieved PR, who demonstrated SD, and who exhibited PD were 25.3 months (95% CI, 11.2–53.0 months), 37.2 months (95% CI, 15.0–111.5 months), and 8.1 months (95% CI, 2.0–23.8 months), respectively (Figure 2). The survival times in the PR and SD groups were significantly superior to those of the PD group (PR versus PD; $p = 0.0197$, SD versus PD; $p = 0.0199$). There were no statistical differences in the survival times between the PR and SD groups ($p = 0.3007$).

The RR and DCR in the 29 patients who received cisplatin were 55.2% and 89.7%, respectively. Of the five patients who received carboplatin instead of cisplatin, one patient achieved PR and three exhibited SD. Among the five patients, the RR was 20.0% and the DCR was 80.0%. The survival curves of both groups are shown in Figure 3. The MSTs in cisplatin and carboplatin group were 23.8 months (95% CI, 15.0–47.6 months) and 7.7 months (95% CI, 2.0–32.3 months), respectively. Although the RR, DCR, and survival time in the cisplatin group showed a favorable tendency compared with those in the carboplatin group, there were no statistical differences, respectively (RR, $p = 0.3328$; DCR, $p = 0.8945$; and survival time, $p = 0.2000$).

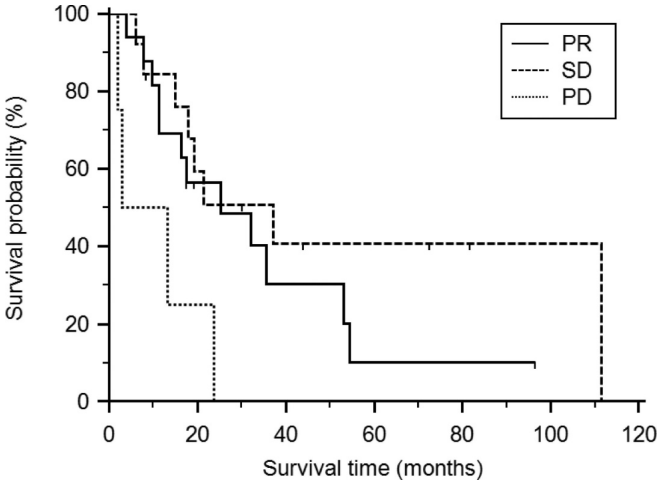

FIGURE 2. Comparison among survival curves of patients who demonstrated PR, SD, and PD. There were significant differences between PR and SD ($p = 0.0197$) and between SD and PD ($p = 0.0199$). PR, partial response; SD, stable disease; PD, progressive disease.

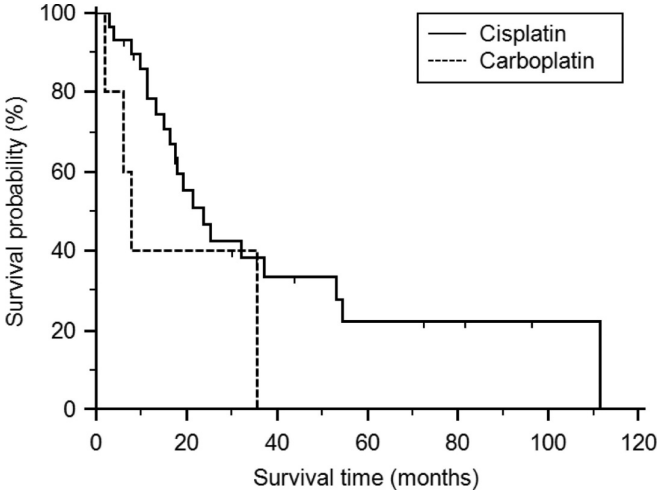

FIGURE 3. Comparison among survival curves of patients who received cisplatin and carboplatin. There was no significant difference between the cisplatin and carboplatin groups ($p = 0.2000$).

Toxicities

The main toxicities of the current chemotherapy in the 34 patients are summarized in Table 3. Grade 3 or 4 leukopenia and neutropenia were observed in 24 patients (70.6%) and 26 patients (76.5%), respectively. There were no patients with grade 3 or more severe anemia. Grade 3 thrombocytopenia was observed in one patient (2.9%). Although four patients (11.8%) developed febrile neutropenia, they were successfully treated with antibiotics and granulocyte colony stimulating factor. The most common nonhematological tox-

TABLE 3. Toxicities of Chemotherapy with Doxorubicin, Vincristine, Cyclophosphamide, and Platinum Compounds

	Grade 3	Grade 4	≥3 (%)
Hematological toxicities			
Leukopenia	19	5	70.6
Neutropenia	12	14	76.5
Anemia	0	0	0
Thrombocytopenia	1	0	2.9
Nonhematological toxicities			
Febrile neutropenia	4	0	11.8
Nausea	7	0	20.6
Vomiting	2	0	5.9
Anorexia	8	0	23.5

icity was anorexia, which was observed in eight patients (23.5%) with a grade of 3. Grade 3 nausea and vomiting were seen in seven (20.6%) and two patients (5.9%), respectively. Those symptoms improved in a short period after the completion of chemotherapy in most of the patients. Overall, the nonhematological toxicities were regarded as mild. There were no treatment-related deaths with the current chemotherapy.

DISCUSSION

The present report describes the efficacy and toxicities of combination chemotherapy with doxorubicin, vincristine, cyclophosphamide, and platinum compounds in 34 patients with unresectable advanced thymic carcinoma. Data on chemotherapy regimens for the treatment of advanced thymic carcinoma are limited, and a standard treatment regimen therefore remains to be established. To the best of our knowledge, the current report is the largest series study analyzing chemotherapy strategies for thymic carcinoma.

With respect to studies on more than 10 patients with thymic carcinoma to evaluate the efficacy of a single regimen, there are currently only two retrospective reports.[12,14] A study evaluating CODE chemotherapy in 12 patients reported a RR of 41.7% and MST of 46 months,[12] and in another study, combination chemotherapy with carboplatin plus paclitaxel in 11 patients had a RR of 36.4% and MST of 22.7 months.[14] There are no published prospective studies designed exclusively for patients with thymic carcinoma, and only two reports addressing thymic tumors (thymoma and thymic carcinoma) are available in the current literature.[15,16] In addition, the two existing reports included a small number of patients with thymic carcinoma (seven and eight patients, respectively). Therefore, the evaluation of chemotherapy for advanced thymic carcinoma based on previous reports is difficult. In this study, combination chemotherapy with doxorubicin, vincristine, cyclophosphamide, and platinum compounds in 34 patients with advanced thymic carcinoma demonstrated a RR of 50.0%. This result could be equivalent or superior to CODE chemotherapy[12] and to carboplatin plus paclitaxel chemotherapy.[14] Although the MST in CODE chemotherapy was reported to be 46 months,[12] the MST in this study was 21.3 months. This difference might be partly due to the predominance of patients with stage IVb disease in our study.

Four patients exhibited PD in this study. After the completion of the chemotherapy series, two patients received the best supportive care because of a deterioration of PS. Sequential radiation was given to two other patients after PD, and only one patient achieved PR as best response. Besides, these two patients received other chemotherapies after the radiotherapy but could not achieve PR in any regimens. Based on these results, thymic carcinoma showing resistance to the current chemotherapy regimen may also show resistance against other chemotherapies. Thus, the poor response to chemotherapy with doxorubicin, vincristine, cyclophosphamide, and platinum compounds might be predictive of reduced chemosensitivity in patients with advanced thymic carcinoma.

Five patients who received carboplatin instead of cisplatin showed a relatively lower RR and shorter MST, compared with patients treated with cisplatin. The median age of the patients in the carboplatin group was 79 years (range, 71–82 years). Two patients had a PS of 2, and four patients had stage IVb disease. These factors might influence the RR and MST, which could explain the differences observed between the two groups. In addition, because of the small number of patients, a comparison between the efficacy of carboplatin and cisplatin is not possible. Differences in the anticancer activity of these two agents in thymic carcinoma need to be investigated further.

With respect to adverse events, although the current regimen showed mild gastrointestinal toxicity, leukopenia and neutropenia were frequently seen. In a study of the efficacy of ADOC chemotherapy in 37 patients with invasive thymoma reported by Fornasiero et al.,[17] 70% of patients developed grade 3 nausea/vomiting according to WHO criteria,[23] with 22% of patients showing grade 3 leukopenia. These results were regarded as opposite to the present results. The differences in gastrointestinal toxicities might be due to differences in the administration of antiemetics, e.g., steroids and 5-hydroxytryptamine 3 receptor antagonists. The differences in hematological toxicities might be related to the age of the patients; the median age in this study was 56 years, and in the study by Fornasiero et al.,[17] it was 40 years. In this study, although leukopenia/neutropenia was the most common adverse event, febrile neutropenia was observed in as few as 11.8%, and there were no treatment-related deaths. The present treatment, therefore, proved to be a well-tolerated chemotherapy regimen.

Meanwhile, it is the age of personalized medicine in the treatment strategies for advanced malignancies today. Targeted therapies for the treatment of thymic carcinoma have been described in some case reports and small case series.[27,28] Successful treatments with sorafenib[29,30] and sunitinib[31] for the patients with chemotherapy-resistant advanced thymic carcinoma have been reported, and a phase II study evaluating the combination of cetuximab with chemotherapy is ongoing in patients with thymoma. Thus, the combination of the current regimen with these molecular targeted agents may bring further benefit to patients with advanced thymic carci-

noma. On the other hand, predictive molecular markers in the treatment for thymic carcinoma should also be examined.

In conclusion, combination chemotherapy with doxorubicin, vincristine, cyclophosphamide, and platinum compounds is a promising treatment strategy for unresectable advanced thymic carcinoma and can be considered an effective regimen for this condition. Nevertheless, similar to the previous reports,[10,11] the present report is also based on a retrospective study, and a definitive conclusion can only be reached through prospective studies. Because of the low incidence rates of this type of carcinoma, the results of this study indicate that multicenter clinical trials of this chemotherapy for unresectable advanced thymic carcinoma are warranted.

REFERENCES

1. Wick MR, Scheithauer BW, Weiland LH, et al. Primary thymic carcinomas. *Am J Surg Pathol* 1982;6:613–630.
2. Suster S, Rosai J. Thymic carcinoma. A clinicopathologic study of 60 cases. *Cancer* 1991;67:1025–1032.
3. Hsu CP, Chen CY, Chen CL, et al. Thymic carcinoma. Ten years' experience in twenty patients. *J Thorac Cardiovasc Surg* 1994;107:615–620.
4. Blumberg D, Burt ME, Bains MS, et al. Thymic carcinoma: current staging does not predict prognosis. *J Thorac Cardiovasc Surg* 1998;115:303–308.
5. Ogawa K, Toita T, Uno T, et al. Treatment and prognosis of thymic carcinoma: a retrospective analysis of 40 cases. *Cancer* 2002;94:3115–3119.
6. Takeda S, Sawabata N, Inoue M, et al. Thymic carcinoma. Clinical institutional experience with 15 patients. *Eur J Cardiothorac Surg* 2004;26:401–406.
7. Yano M, Sasaki H, Yokoyama T, et al. Thymic carcinoma: 30 cases at a single institution. *J Thorac Oncol* 2008;3:265–269.
8. Weide LG, Ulbright TM, Loehrer PJ Sr, et al. Thymic carcinoma. A distinct clinical entity responsive to chemotherapy. *Cancer* 1993;71:1219–1223.
9. Nakamura Y, Kunitoh H, Kubota K, et al. Platinum-based chemotherapy with or without thoracic radiation therapy in patients with unresectable thymic carcinoma. *Jpn J Clin Oncol* 2000;30:385–388.
10. Kitami A, Suzuki T, Kamio Y, et al. Chemotherapy of thymic carcinoma: analysis of seven cases and review of the literature. *Jpn J Clin Oncol* 2001;31:601–604.
11. Koizumi T, Takabayashi Y, Yamagishi S, et al. Chemotherapy for advanced thymic carcinoma: clinical response to cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC chemotherapy). *Am J Clin Oncol* 2002;25:266–268.
12. Yoh K, Goto K, Ishii G, et al. Weekly chemotherapy with cisplatin, vincristine, doxorubicin, and etoposide is an effective treatment for advanced thymic carcinoma. *Cancer* 2003;98:926–931.
13. Maruyama R, Suemitsu R, Okamoto T, et al. Persistent and aggressive treatment for thymic carcinoma. Results of a single-institute experience with 25 patients. *Oncology* 2006;70:325–329.
14. Igawa S, Murakami H, Takahashi T, et al. Efficacy of chemotherapy with carboplatin and paclitaxel for unresectable thymic carcinoma. *Lung Cancer* 2010;67:194–197.
15. Oshita F, Kasai T, Kurata T, et al. Intensive chemotherapy with cisplatin, doxorubicin, cyclophosphamide, etoposide and granulocyte colony-stimulating factor for advanced thymoma or thymic cancer: preliminary results. *Jpn J Clin Oncol* 1995;25:208–212.
16. Loehrer PJ Sr, Jiroutek M, Aisner S, et al. Combined etoposide, ifosfamide, and cisplatin in the treatment of patients with advanced thymoma and thymic carcinoma: an intergroup trial. *Cancer* 2001;91:2010–2015.
17. Fornasiero A, Daniele O, Ghiotto C, et al. Chemotherapy for invasive thymoma. A 13-year experience. *Cancer* 1991;68:30–33.
18. Travis WD, Brambilla E, Muller-Hermelink HK, et al. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon: IARC press, 2004.
19. Masaoka A, Monden Y, Nakahara K, et al. Follow-up study of thymomas with special reference to their clinical stages. *Cancer* 1981;48:2485–2492.
20. World Health Organization. WHO Handbook for Reporting Results of Cancer Treatment, Vol. 48. Geneva: WHO offset publication, 1979.
21. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–216.
22. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
23. Miller AB, Hoogstraten B, Staquet M, et al. Reporting results of cancer. *Cancer* 1981;47:207–214.
24. National Cancer Institute: Common Toxicity Criteria (CTC) Version 2.0 [National Cancer Institute Web site], 1999. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Accessed March 1, 2011.
25. Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 [National Cancer Institute Web site], 2003. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Accessed March 1, 2011.
26. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649–655.
27. Strobel P, Hohenberger P, Marx A. Thymoma: molecular pathology and targeted therapy. *J Thorac Oncol* 2010;5:S286–S290.
28. Rajan A, Giaccone G. Targeted therapy for advanced thymic tumors. *J Thorac Oncol* 2010;5:S361–S364.
29. Bisagni G, Rossi G, Cavazza A, et al. Long lasting response to the multikinase inhibitor bay 43–9006 (sorafenib) in a heavily pretreated metastatic thymic carcinoma. *J Thorac Oncol* 2009;4:773–775.
30. Li XF, Chen Q, Huang WX, et al. Response to sorafenib in cisplatin-resistant thymic carcinoma: a case report. *Med Oncol* 2009;26:157–160.
31. Strobel P, Bargou R, Wolff A, et al. Sunitinib in metastatic thymic carcinomas: laboratory findings and initial clinical experience. *Br J Cancer* 2010;103:196–200.