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was a 45-year-old man admitted with myasthenia gravis. Both patients had nonresectable thymomas (stage IVa) because of invasion of the aorta, pulmonary artery, or both, and dissemination to the pericardium. They initially received two cycles of chemotherapy consisting of adriamycin (40 mg/m², day 1), cisplatin (50 mg/m², day 1), vincristine (0.6 mg/m², day 3), and cyclophosphamide (700 mg/m², day 4) at 3-week intervals. Four weeks later, they were administered high-dose etoposide (300 mg/m², days 1 to 5) followed by granulocyte colony-stimulating factor (G-CSF) [50 µg/m²/d] subcutaneously to mobilize stem cells into the blood. After two additional cycles of adriamycin, cisplatin, vincristine, and cyclophosphamide (ADOC), the patients received high-dose ifosfamide (1.5 g/m², days 1 to 4), carboplatin (400 mg/m², days 3 to 5), and etoposide (200 mg/m², days 1 to 5) followed by PBSCT. They were administered G-CSF (50 µg/m²/d) after PBSCT, with subsequent rapid recovery of neutrophil and platelet level. The tumors shrank remarkably, and could be excised completely in both patients. Postoperatively, 50 Gy of irradiation was administered. Disease-free status has been maintained for 5 years in the first patient and 2 years in the second patient. Our findings suggest that high-dose ifosfamide, carboplatin, and etoposide followed by PBSCT in combination with an ADOC regimen, surgery, and radiotherapy is very effective and well tolerated in patients with advanced nonresectable thymoma.

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Key words: high-dose chemotherapy; invasive thymoma; multidisciplinary therapy; peripheral blood stem cell transplantation

Abbreviations: ADOC = adriamycin, cisplatin, vincristine, and cyclophosphamide; ICE = ifosfamide, carboplatin, and etoposide; G-CSF = granulocyte colony-stimulating factor; PAC = cisplatin, doxorubicin, and cyclophosphamide; PBSCT = peripheral blood stem cell transplantation

Multidisciplinary Therapy Including High-Dose Chemotherapy Followed by Peripheral Blood Stem Cell Transplantation for Invasive Thymoma*

Yoshinobu Iwasaki, MD, PhD; Shuji Ohsugi, MD; Yoshizumi Takemura, MD; Kazuhiro Nagata, MD; Hidehiko Harada, MD; and Masao Nakagawa, MD, PhD

We describe two patients with invasive thymomas who responded to high-dose chemotherapy followed by peripheral blood stem cell transplantation (PBSCT) combined with surgery and radiotherapy. The first patient was a 42-year-old man admitted to the hospital with chest pain, and the second patient

Thymomas are rare, slowly growing neoplasms with peak incidence at approximately 50 years of age.¹ Thymomas are histologically classified into predominantly epithelial, predominantly lymphocytic, and mixed lympho-epithelial types,² regardless of cytologic abnormalities of the neoplastic epithelial cells. Their malignant behavior is defined according to macroscopic and microscopic signs of invasiveness, not histologic criteria. The presence of tumor invasion is considered the most important predictor of future behavior³ and forms the basis for the clinical staging system described by Masaoka et al.⁴ After total resection, noninvasive thymomas carry a good prognosis, with 10-year survival rates ranging from 67 to 80%.^{3,5} Because postoperative relapse of noninvasive thymomas is rare,^{1,6} surgery alone is the treatment of choice. In contrast, invasive thymomas have a considerably worse outcome. Large invasive thymomas are difficult to resect completely. Radiation is sometimes administered preoperatively to facilitate resection of bulky tumors and can be useful for salvage therapy after unsuccessful surgical treat-

*From the Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan.

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Correspondence to: Yoshinobu Iwasaki, MD, Second Department of Medicine, Kyoto Prefectural University of Medicine, 465 Kawaramachi Hirokoji, Kamigyo-ku, Kyoto 602, Japan; e-mail: yiwasaki@koto.kpu-m.ac.jp

ment.⁷ Radiotherapy also plays an important role in the postoperative management of completely resected invasive thymomas, but is associated with a high frequency of pleural recurrence in stage III disease. More effective adjuvant strategies are thus needed.⁸ Chemotherapy is also required in patients with stage III and IV invasive thymomas. Combination chemotherapy is usually effective and has been used preoperatively to facilitate resection of locally advanced disease.⁹ Peripheral blood stem cell transplantation (PBSCT) has been widely used to manage the hematologic toxicity caused by high-dose chemotherapy in patients with chemosensitive solid tumors.¹⁰ We describe two patients with invasive thymomas (stage IVA) who responded to high-dose chemotherapy followed by PBSCT, combined with conventional chemotherapy, radiotherapy, and surgery.

CASE REPORTS

Case 1

A 42-year-old man was admitted to the hospital because of chest pain. A large mass in the anterior mediastinum was seen on the chest radiograph and confirmed by CT (Fig 1). Surgery was performed, but the tumor was nonresectable because it had invaded the aorta and pulmonary artery and disseminated to the pericardium. Invasive thymoma (stage IVA, lymphocytic predominant histology) was diagnosed. The patient initially received two cycles of chemotherapy consisting of adriamycin (40 mg/m^2) and cisplatin (50 mg/m^2) administered on day 1, vincristine (0.6 mg/m^2) on day 3, and cyclophosphamide (700 mg/m^2) on day 4, at 3-week intervals. Four weeks after the first two cycles of adriamycin, cisplatin, vincristine, and cyclophosphamide (ADOC), he was administered 300 mg/m^2 of etoposide for 5 days, followed by granulocyte colony-stimulating factor (G-CSF) [$50 \text{ } \mu\text{g/m}^2$] subcutaneously to mobilize stem cells into the blood. The number of WBCs exceeded $5,000/\mu\text{L}$ on day 17, and peripheral blood stem cell collection was performed on days 17 and 18. A total of 8.54×10^5 granulocyte-macrophage colony-forming units per kilogram was obtained. After two additional cycles of ADOC, he received high-dose ifosfamide, carboplatin, and etoposide (ICE) therapy. Ifosfamide was administered at $1.5 \text{ g/m}^2/\text{d}$ as a 3-h IV infusion on days 1 to 4. Carboplatin was administered

at $400 \text{ mg/m}^2/\text{d}$ as a 6-h IV infusion on days 3 to 5. Etoposide was administered at $200 \text{ mg/m}^2/\text{d}$ as a continuous infusion on days 1 to 5. Mesna, 400 mg/m^2 , was administered as a 1-h IV infusion 1 h before and 4 h and 8 h after ifosfamide administration. Forty-eight hours after the end of chemotherapy, 2.45×10^5 granulocyte-macrophage colony-forming units per kilogram was reinfused and G-CSF was administered subcutaneously a dosage of $50 \text{ } \mu\text{g/m}^2/\text{d}$. Posttransplant neutropenia $< 500/\mu\text{L}$ and thrombocytopenia $< 50,000/\mu\text{L}$ lasted for 9 days and 14 days, respectively. The tumor was confirmed to have shrunk remarkably on a chest radiograph and CT scan (Fig 2). Three months later, total surgical resection was performed, and a complete response was confirmed pathologically. Postoperatively, 50 Gy of irradiation was administered. Disease-free status has continued for 5 years.

Case 2

A 45-year-old man was admitted to the hospital because of myasthenia gravis with a large mass in the anterior mediastinum (Fig 3). Surgery was performed, but the tumor was unresectable because it had invaded the aorta and disseminated to the pericardium. Invasive thymoma (stage IVA, mixed lymphoepithelial histology) was diagnosed. The patient initially received two cycles of ADOC at 3-week intervals. Four weeks later, he was administered 300 mg/m^2 of etoposide for 5 days followed by G-CSF ($50 \text{ } \mu\text{g/m}^2$) subcutaneously to mobilize stem cells into the blood. The number of WBCs was $> 5,000/\mu\text{L}$ on day 21, and peripheral blood stem cell collection was performed on days 21 and 22. A total of 25.9×10^6 CD34-positive cells per kilogram was obtained. After two additional cycles of ADOC, he received high-dose ICE therapy. Forty-eight hours after the end of chemotherapy, 2.4×10^6 CD34-positive cells per kilogram was reinfused, and G-CSF was administered subcutaneously at a dose of $50 \text{ } \mu\text{g/m}^2/\text{d}$. Posttransplant neutropenia $< 500/\mu\text{L}$ and thrombocytopenia $< 50,000/\mu\text{L}$ lasted for 7 days and 11 days, respectively. The tumor was demonstrated to have shrunk markedly on a chest radiograph and CT scan (Fig 4). Three months later, total surgical resection was performed. Postoperatively, 50 Gy of irradiation was administered. Disease-free status has been maintained for 2 years.

DISCUSSION

Recurrence after surgery for noninvasive thymoma is rare (0 to 3.8%)^{1,6}; consequently, most patients do not

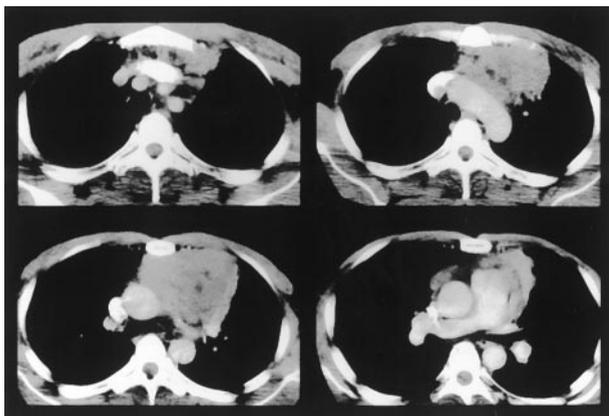


FIGURE 1. Chest CT scan on hospital admission (case 1). A large solid tumor in the anterior mediastinum invades the lung.

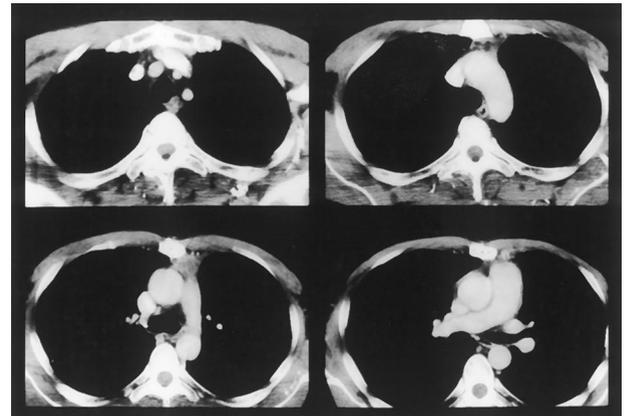


FIGURE 2. Chest CT scan after four cycles of ADOC regimen and high-dose ICE (case 1). The tumor had shrunk remarkably.

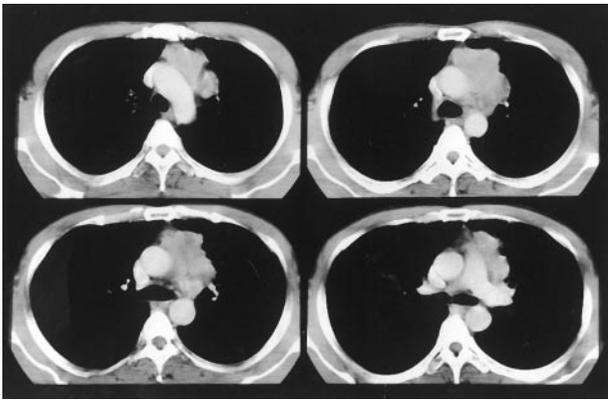


FIGURE 3. Chest CT scan on hospital admission (case 2). A large solid tumor in the anterior mediastinum invades the ascending aorta.

receive postoperative adjuvant treatment. In contrast, invasive thymomas have a much worse prognosis.¹¹ Large invasive thymomas with invasion of major vessels or cardiac structures are difficult to resect completely. Despite improved surgical techniques, radical resection is feasible in only approximately one half of patients with stage III disease and is usually impractical in those with stage IV disease.¹² Although most thymomas are considered to follow an indolent course, with recurrence limited to the thorax, invasive thymomas have been associated with distant metastases, most commonly to the liver, bone, kidney, and extrathoracic lymph nodes. Arriagada et al¹³ reported that distant metastasis was the primary cause of death (64%) in a retrospective review of patients with invasive thymomas. Systemic chemotherapy thus plays a very important role in the treatment of invasive thymomas.

Chemotherapy is effective against most invasive thymomas and can be used preoperatively to improve resectability.⁹ Chemotherapeutic regimens containing platinum are usually more effective than regimens without platinum.¹⁴ In a review of platinum-containing regimens, Loehrer et al¹⁵ reported the response to combination therapy with

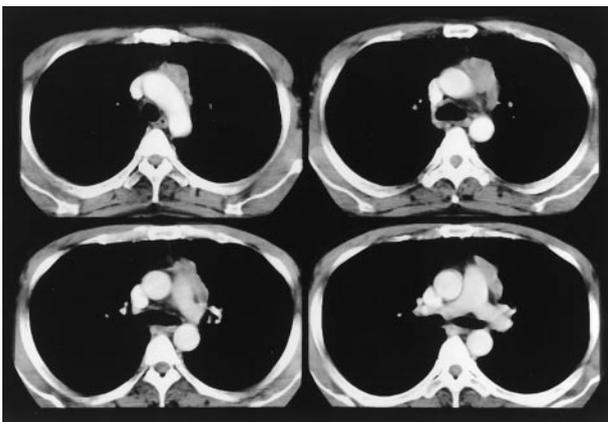


FIGURE 4. Chest CT scan after four cycles of ADOC regimen and high-dose ICE (case 2). The tumor had shrunk markedly.

cisplatin, doxorubicin, and cyclophosphamide (PAC) in invasive thymoma. In their study, 20 patients with stage III or IV invasive thymomas received PAC therapy at 3-week intervals. Three complete and 11 partial responses were confirmed (overall response rate, 70%). The median duration of response was 13 months, and the median survival time was 59 months.

Combination therapy with etoposide, ifosfamide, and cisplatin was evaluated in patients with invasive thymomas or thymic carcinomas and was reported by Loehrer et al.¹⁶ In their report, 28 patients with invasive thymoma or thymic carcinoma received etoposide, ifosfamide, and cisplatin at 3-week intervals for four cycles. There were no complete responses and nine partial responses.

Fornasiero et al¹⁷ reported on the response to ADOC therapy. In their study, 37 patients with stage III or IV invasive thymomas received ADOC therapy at 3-week intervals. The overall response rate was 92%, with a complete response rate of 43%.

A few studies have used high-dose chemotherapy to treat invasive thymoma. Hanna et al¹⁸ reported that high-dose carboplatin and etoposide followed by PBSCT was effective with acceptable toxicity in patients with recurrent thymoma. Our patients received four cycles of the ADOC regimen at 3-week intervals and thereafter high-dose ICE followed by PBSCT. We used ICE for high-dose chemotherapy because these drugs have been demonstrated to be safe and effective in patients with invasive thymomas.^{19–21} A complete response was obtained in the first case, and a partial response was obtained in the second.

Several studies have assessed the response to combination chemotherapy followed by radiotherapy in invasive thymoma. Loehrer et al²² reported encouraging results in patients administered a PAC regimen combined with radiation therapy. In their study, 23 patients received two to four cycles of PAC therapy at 3-week intervals followed by a total dose of 54 Gy to the primary tumor and regional lymph nodes in patients who had a stable, partial, or complete response to chemotherapy. There were 5 complete and 11 partial responses to chemotherapy (overall response rate, 70%). The median time to treatment failure was 93 months, and the median survival time was 93 months. The 5-year survival rate was 53%.

The role of radiation after complete resection of invasive thymomas is controversial. Curran et al²³ reported that 53% of patients treated with surgery alone had recurrence within 5 years. The rate of local failure was 0% after complete resection with radiation and 21% after subtotal resection or biopsy with radiation.²³ In our patients, complete resection could be performed after high-dose ICE therapy, and irradiation was administered subsequently. The optimal dose of irradiation for invasive thymomas remains unclear. Cox²⁴ reported that better locoregional control was obtained at a dose \geq 60 Gy. Mornex et al²⁵ showed that a 50-Gy dose adequately controlled tumor recurrence after complete resection. Our patients also received 50 Gy after complete resection.

Our findings suggest that high-dose ICE followed by PBSCT in combination with ADOC therapy, surgery, and radiotherapy is highly effective and well tolerated in patients with advanced nonresectable thymoma. Invasive

thymomas may be cured by such multidisciplinary therapy, including high-dose chemotherapy followed by PBSCT.

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Subarachnoid Pleural Fistula Due to Penetrating Trauma*

Case Report and Review of the Literature

Christian Lloyd, MD; and Steven A. Sahn, MD, FCCP

We describe a case of a 30-year-old man who developed a recurrent pleural effusion after sustaining a gunshot wound to the left side of his chest with subsequent complete paralysis at the T2 level. Subarachnoid-pleural fistulas have rarely been reported as complications of penetrating and blunt trauma, thoracic surgery, as well as spinal surgery. Concomitant injuries may overshadow or complicate the diagnosis of subarachnoid-pleural fistulas. The diagnosis should be considered in any patient with a pleural effusion that is associated with severe neurologic injury, as the fistula rarely heals without surgical intervention and may lead to CNS infection or pneumocephalus.

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Key words: β_2 -transferrin; CNS infections; CT scanning; hemothorax; laminectomy; myelography; pleural effusion; spinal cord trauma

Abbreviation: CSF = cerebral spinal fluid

*From the Division of Pulmonary and Critical Care Medicine, Allergy and Clinical Immunology, Medical University of South Carolina, Charleston, SC.

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Correspondence to: Steven A. Sahn, MD, FCCP, Professor of Medicine and Director, Division of Pulmonary and Critical Care Medicine, Allergy and Clinical Immunology, Medical University of South Carolina, 96 Jonathan Lucas St, Suite 812, PO Box 250623, Charleston, SC 29425; e-mail: sahnsa@muscc.edu