Retreatment of Recurrent Invasive Thymoma With Platinum, Doxorubicin, and Cyclophosphamide*

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Invasive thymoma recently has been shown to be sensitive to combination chemotherapy and in some cases to be relatively indolent. Two cases of extensive thymoma which responded to primary treatment with a combination of a platinum compound (carboplatin or cisplatin), doxorubicin (Adriamycin), and cyclophosphamide (or PAC) are described. Tumor progression occurred 14 (case 1) and 60 months (case 2) after completion of initial PAC therapy and was treated with the same regimen resulting in a second remission, which lasted 6 months in case 1 and is continuing at 8 months in case 2. Similar reports of secondary responses using the same chemotherapy have been described in breast, lung, and ovarian cancers, as well as in Hodgkin's lymphomas. Our observations suggest that retreatment with the same platinum-based regimen should be considered in patients who have progressive thymomas following a previous chemotherapeutic response and a disease-free interval of greater than 12 months. (CHEST 1996; 110:1115-17)

Key words: chemotherapy; malignant thymoma; salvage therapy

Abbreviations: PAC-platinum, doxorubicin (Adriamycin), and cyclophosphamide

Thymomas are rare tumors of the anterior superior mediastinum, accounting for about 15% of all mediastinal masses. Although thymomas are histologically benign and grow indolently, some invade the surrounding structures and behave as malignant tumors. Only 40% of thymomas are completely encapsulated, with no evidence of microscopic invasion. Traditional management of invasive thymomas generally involves surgical resection and radiotherapy, but recently cytotoxic chemotherapy, particularly regimens using cisplatin, doxorubicin (Adriamycin), and cyclophosphamide (PAC), has been shown to produce response rates of 70 to 91.8%. In addition to being relatively sensitive to chemotherapy, it appears that invasive thymomas are somewhat indolent with some incurable patients surviving for years. Therefore, some patients who initially responded to chemotherapy will be candidates for salvage chemotherapy.

This is a report of two patients with unresectable invasive thymoma who initially responded to a course of a platinum compound, PAC, and whose recurrence again responded to PAC. These appear to be the first reported cases of thymoma in which the same platinum-based regimen achieved a secondary remission.

Case Reports

Case 1

A 26-year-old Asian man was first seen at our institution in November 1978 with a diagnosis of myasthenia gravis requiring therapy with prednisone and subsequently a thymectomy in December 1978. During the next decade, he suffered recurrent upper respiratory tract infections and myasthenic exacerbations. He was readmitted to this hospital in May of 1992 for productive cough and fever. A chest radiograph done at this time showed an anterior mediastinal mass, and a subsequent CT scan confirmed the presence of recurrent mediastinal thymoma with pleural metastasis which was later confirmed by mediastinoscopy and biopsy. In late May, an open thoracotomy was performed, which showed tumor involvement of the parietal pleura and both vagus and phrenic nerves, precluding complete resection of the tumor. The patient was therefore offered and agreed to treatment with chemotherapy consisting of four courses (every 21 days) of a combination of carboplatin at 300 mg/m², doxorubicin at 50 mg/m², and cyclophosphamide at 500 mg/m² beginning on June 7, 1992. Prior to starting chemotherapy and throughout the treatment period, the patient received prednisone for myasthenia gravis and asthma with daily oral doses averaging 10 to 15 mg. The patient eventually completed chemotherapy on September 28, 1992. Chest radiographs taken immediately before and after chemotherapy revealed a reduction in size of the tumor from a 5x4-cm irregularly sized mass to an indistinct haziness over the left lung field. He continued to remain in clinical remission until December 1993 when he was readmitted for a malignant right-sided pleural effusion requiring chest tube drainage and pleurodesis. The chest radiograph at this time revealed a 6.5-cm pleural based mediastinal mass in the left hemithorax consistent with recurrent thymoma. A chest CT showed multiple large inhomogeneous pleural-based soft tissue masses in the left hemithorax and the anterior mediastinum (Fig 1). At this time, the patient received another course of the PAC regimen at adjusted doses: carboplatin, 300 mg/m²; doxorubicin, 40 mg/m²; and cyclophosphamide, 400 mg/m²; the therapy was administered at 4-week intervals for a total of 4 cycles beginning in late December 1993. Another chest CT scan in April 1994 showed a reduction in the size of the mediastinal mass from 9x10 cm at the widest dimensions to 7x9 cm. The patient’s myasthenia gravis has remained remission for 16 years since the completion of chemotherapy.

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A 54-year-old white man without any significant past medical history presented to our institution in June 1989 with a 4-year history of vague anterior neck swelling and discomfort. A neck MRI at this time demonstrated a large solid soft-tissue mass in the lower area of the left side of the neck with mediastinal extension, tracheal deviation, and left innominate vein occlusion. A chest radiograph suggested a right pleural effusion. He was subsequently admitted to the hospital, and a needle biopsy of the neck mass demonstrated malignant thymoma. He received 3 courses (every 21 days) of cyclophosphamide (500 mg/m²), doxorubicin (50 mg/m²), and cisplatin (50 mg/m²) from July 28 to September 20, 1989, resulting in a 50% reduction in the tumor size and resolution of the pleural effusion. A thymectomy was performed in October 1989 with resection of all visible tumor. He had mediastinal radiotherapy (60 Gy) thereafter, completing treatment in December 1989. He did well for 5 years until February 1995 when he presented with cough and hoarseness. An ear, nose, and throat evaluation revealed left vocal cord paralysis, tracheal deviation to the right, and a palpable mass in the suprasternal notch adjacent to the left sternocleidomastoid joint. A CT scan of the neck and chest demonstrated an ill-defined 3.0×2.5-cm mass to the left of the trachea at the thoracic inlet and a 1.5×2.0-cm anterior mediastinal lymph node. Recurrent thymoma was confirmed by ultrasound-guided biopsy of the tumor. He began 4 courses (every 28 days) of carboplatin (300 mg/m²), doxorubicin (40 mg/m²), and cyclophosphamide (400 mg/m²) from February to June 1995. A postchemotherapy chest CT scan showed that the tumor and anterior mediastinal lymph node were no longer detectable. A positron emission tomography scan done 2 months later revealed no evidence of malignancy. He continues to do well and remains in remission as of February 1996, 8 months after his remission was noted.

DISCUSSION

Recently, it has become apparent that invasive thymoma is relatively sensitive to combination chemotherapy and that survival is relatively long. In two fairly large series using the PAC regimen or a combination of cisplatin, doxorubicin, vincristine, and cyclophosphamide, overall response rates ranged from 70 to 91.8%, with median durations of response averaging 11.9 months and median survival ranging from 15 to 37.7 months.3,4 Recently, PAC with etoposide and concurrent granulocyte colony-stimulating factor had been used for advanced thymoma or thymic cancer with a reported 42.9% response rate (all partial remissions) but with significant bone marrow toxicity.5 The PAC regimen was chosen for our patients because of the favorable response rates noted. We substituted carboplatin for cisplatin for easier outpatient administration. The concurrent use of oral prednisone in case 1 was not a likely confounding factor because his tumor progressed during low-dose steroid therapy.

Our patients developed progressive thymoma after initially responding to combination chemotherapy consisting of cyclophosphamide, doxorubicin, and carboplatin. The standard treatment options for this situation, in order of decreasing effectiveness, are a subsequent surgical resection, radiotherapy, and corticosteroid use. There are reports of small prospective trials of second-line chemotherapy using various regimens (single or in combination) with disappointing results.3,7 The role of low-dose oral etoposide in the management of recurrent thymoma has not been evaluated in clinical trials although there are reports of some efficacy as first-line therapy in combination with cisplatin.8 We elected to use the same chemotherapeutic regimen to treat our patients’ recurrences because their disease had responded to the PAC regimen previously, because the disease-free interval was greater than 6 months, and because there was evidence that secondary responses occurred with the same regimen in lung, breast, and ovarian cancers as well as in Hodgkin’s lymphomas.9-11 Higher response rates were noted when the disease-free intervals were greater than 12 months in breast cancer,14 24 months in epithelial ovarian cancer,15 and 12 months in Hodgkin’s lymphoma.11 The disease-free intervals in our patients were 14 and 60 months, respectively.

Several investigators have reported cases of second-line chemotherapy using different regimens with mixed results.16,17 In three patients who had relapses following therapy with a regimen of combination cisplatin, doxorubicin, vincristine, and cyclophosphamide, treatment with cisplatin, etoposide, and ifosfamide resulted in stable disease in two patients.3 Only one other report of a response to salvage chemotherapy with the same regimen was noted in the medical literature. Kosmidis et al18 reported a case of unresectable invasive thymoma treated with radiotherapy with an 80% response but 4 months later there was disease progression. Local recurrence was treated with cyclophosphamide, doxorubicin, and vincristine, which produced a partial response. The patient refused further treatment against medical advice. Nine months later, the patient presented with renal and abdominal lymph node metastasis. This was treated with the same combination of drugs, again producing a significant improvement consisting of a more than 50% reduction in tumor bulk, noted both clinically and radiographically. The patient eventually had a relapse 9 months after re-initiation of chemotherapy and died of renal failure.
The results observed in our patients showed that secondary responses to chemotherapy can be achieved using the same platinum-based regimen. Our observations suggest that it is reasonable to retreat thymoma patients with the same regimen provided that there has been a previous favorable response and that the disease-free interval is greater than 12 months.

REFERENCES

Chest Pain in an Aspirin-Sensitive Asthmatic Patient*

Eosinophilic Esophagitis Causing Esophageal Dysmotility

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We describe a case of eosinophilic esophagitis in a 38-year-old man with aspirin-sensitivity asthma which presented as noncardiac chest pain. Manometric measurements demonstrated tertiary contractions. Biopsies showed a dense eosinophilic infiltrate in the mucosa. There was no response to therapy for reflux. Symptoms quickly resolved with corticosteroid therapy. Subsequent manometric values recorded after corticosteroid therapy showed resolution of the dysmotility. Biopsies showed normal mucosa. Adults with noncardiac chest pain should receive further investigation if reflex therapy fails to resolve the symptoms. (CHEST 1996; 110:1117-20)

Key words: esophageal spasm

The most common esophageal symptoms in asthmatic subjects are due to gastroesophageal reflux. Reflux may worsen the asthma, and control of the asthma may not occur until the reflux is adequately managed. Many medications used to treat asthma decrease lower esophageal sphincter tone. This may contribute to the reflux symptoms. Therefore, reflux is commonly seen in both children and adults with asthma, both as a cause of the asthma and as a consequence of treatment.

In this case report, we describe an asthmatic patient with a long history of reflux who develops a new chest pain syndrome related to, but distinct from, the reflux. Initial attempts to manage the reflux did not decrease the pain. A diagnosis of dysmotility was made by esophageal manometric measurements. Mucosal biopsy demonstrated eosinophilic esophagitis. The patient promptly responded to corticosteroid treatment.

CASE REPORT

A 38-year-old man with asthma was seen for a 1-month history of atypical chest pain. The pain was substernal, squeezing, and did not radiate. The pain often awoke the patient at night. Sometimes the pain was preceded by heartburn. It was partially relieved by antacids and swallowing cold liquids. The episodes of pain would last from 15 min to several hours. There was no shortness of breath or diaphoresis. There was no exertional component. The chest pain was preceded by a 2-week history of increased nasal discharge. There were no new medications, new foods, or changes in diet.

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