Combined heart and lung transplantation for unresectable primary cardiac sarcoma

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Objective: The prognosis for patients with primary cardiac sarcoma is poor. Median survival is less than 10 months, especially when complete surgical excision is not feasible. Removal of all cardiopulmonary structures involved by tumor followed by orthotopic allotransplantation has been proposed to improve long-term survival.

Methods: From 1996 through 1999, we performed combined heart and lung resection followed by en bloc heart and bilateral lung transplantation in 4 patients (2 men and 2 women): 2 with inoperable pulmonary arterial sarcoma and 2 with left atrial sarcoma extending into the pulmonary vein.

Results: Median age at diagnosis was 39 years (range 37-45 years). All 4 patients were given chemotherapy before transplantation: doxorubicin and ifosfamide in 2 cases, and doxorubicin, ifosfamide, mesna, and dacarbazine in 2 cases. There were no operative deaths. Median survival after transplantation was 31 months (range 5-49 months). All patients had tumor recurrence: local recurrence in the chest (n = 1) and distant metastases in the brain (n = 2) and abdomen (n = 1). One patient remains alive 49 months after disease progression with cerebral metastasis as the only site of recurrence treated with whole-brain irradiation, resection, and stereotactic radiosurgery.

Conclusions: Combined heart and lung transplantation is a technically feasible treatment for highly selected patients with localized advanced primary cardiac sarcomas. The high incidence of metastatic disease, however, limits its utility.

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Primary cardiac sarcomas are rare clinical entities,^{1,2} with an incidence at autopsy of 0.0001%.³ Soft tissue sarcoma is the most common malignant neoplasm of the heart, pericardium, and great vessels.^{4,5} These tumors usually cause symptoms as a result of anatomic obstruction of blood flow, necessitating resection to relieve symptoms and prevent early death.⁶

Outcomes after treatment of primary cardiac sarcoma have been extremely poor, especially when surgical excision is not feasible.^{5,7,8} In these instances, median survival is generally 10 months or less.⁸⁻¹⁰ There are no proven benefits to chemotherapy and radiotherapy.⁵

In a few cases, a curative surgical approach consisting of cardiectomy followed by orthotopic transplantation has been attempted to provide long-term survival, but only anecdotal reports of this aggressive approach were available for review.^{1,11-19} These reports have dealt with transplantation of the heart only, rather than the heart and lungs. In general, favorable results have occurred only when the cardiac surgical margins were free of tumor. If the surgical margins were involved with tumor, disease progression and death ensued despite adjuvant chemotherapy.

In 1996, we began to investigate whether combined heart and lung resection followed by en bloc heart and bilateral lung transplantation might be curative in those instances of primary cardiac sarcomas in which the tumor clearly extended beyond the cardiac borders of cardiectomy. During the next 2 years, we performed this procedure in 4 patients, 2 with inoperable pulmonary arterial sarcomas and 2 with left atrial sarcomas extending into the pulmonary veins.

Clinical Summaries

Case 1

A 40-year-old previously healthy man reported dyspnea and hemoptysis. Chest radiography showed a left hilar mass. During thoracic exploration, an intimal sarcoma of the pulmonary artery was diagnosed. The patient underwent left pneumonectomy, resection of the pulmonary valve and pulmonary artery, and insertion of a pulmonary homograft from the right ventricular outflow tract to the right pulmonary artery. Tumor was present in the margins of the resection. He received 2 cycles of chemotherapy with mesna, doxorubicin, ifosfamide, and dacarbazine and radiation therapy. He was referred for consideration of possible heart-lung transplantation. Preoperative scans of head, chest, abdomen, pelvis, and bone showed no evidence of metastatic tumor. Two months after referral, the patient underwent combined heart and lung transplantation. Pathologic examination revealed intimal sarcoma in the right ventricular endocardium and right pulmonary artery. There were no signs of pulmonary parenchymal metastasis. The postoperative recovery was uneventful. After discharge, the patient regained excellent exercise tolerance and returned to full-time employment. Three years after transplantation, he reported severe abdominal pain, and small-bowel obstruction was diagnosed. Exploratory laparotomy demonstrated intussusception of the jejunum with two polypoid lesions serving as lead points. Resection of the lesions demonstrated intimal sarcoma identical to the previous pulmonary artery tumor. The patient was treated with ifosfamide chemotherapy and sequentially with two investigational drugs, temozolomide and the cell surface phospholipase inhibitor CT 2584 (Cell Therapeutics Inc, Seattle, Wash). However, he continued to have extensive abdominal pain and only minimal tumor regression. The patient died 4 years after transplantation of massive intra-abdominal tumor bleeding.

Case 2

A 39-year-old previously healthy woman had dyspnea and chest pain, and pulmonary arterial thrombosis was diagnosed. She underwent thromboembolectomy, which revealed spindle cell sarcoma of the pulmonary artery extending into both right and left lobar arteries. The patient underwent 6 cycles of doxorubicin and ifosfamide chemotherapy after the operation. She was referred for heart-lung transplantation. Preoperative scans revealed no evidence of disease at the time of listing. However, on the day before transplantation, she reported weakness in her left hand. Magnetic resonance imaging of the brain was performed at her local institution. On the following day, she underwent heart-lung transplantation. Pathologic examination revealed a long, fimbriate tumor extending into both pulmonary arteries. The results of the magnetic resonance imaging, which became known after the operation,

showed a 2-cm lesion in the left frontal cortex and a second, smaller lesion in the cerebellum. The patient's postoperative recovery was without complication, and on the 10th postoperative day she began whole-brain radiation. Two months after transplantation, she underwent left craniotomy for resection of the parietal tumor. Subsequently, the patient underwent stereotactic focus radiosurgery for the right cerebellar lesion. She resumed full-time activities with excellent exercise tolerance. She has had minimal residual neurologic deficits related to the craniotomy. At present (49 months after transplantation), the patient remains alive with cerebral metastasis as the only site of tumor recurrence. Four years after transplantation, dyspnea on exertion developed, and bronchiolitis obliterans syndrome has been diagnosed.

Case 3

A 37-year-old previously healthy woman had dyspnea on exertion and hemoptysis. Chest radiography showed a large left infrahilar mass. She underwent exploratory left thoracotomy. There was a large tumor arising in the left atrium and extending into the left pulmonary veins. The pathologic examination confirmed a high-grade spindle cell sarcoma. The patient completed 5 cycles of chemotherapy with mesna, doxorubicin, ifosfamide, and dacarbazine and was referred for heart-lung transplantation. Preoperative scans showed no evidence of distant tumoral spread. Four months after listing, she underwent heart-lung transplantation. At the time of transplantation, a large tumor mass extended from the left atrium into the left pulmonary veins, into the left lung, and nearly out to the pleural surface of the left lung. The tumor was removed en bloc, but function of the left hemidiaphragm was sacrificed. The immediate postoperative course was complicated by poor clearance of secretions in the left lower lobe. After discharge, the patient returned to full activity. However, 6 months after the operation a recurrent tumor mass developed in the left lower lobe. Biopsy revealed high-grade spindle sarcoma, identical to that explanted from the heart and lungs. The patient underwent left lower lobectomy with rib and diaphragm resection. Pathologic examination showed tumor invasion of the ribs and pleura. After resection, a course of radiation therapy to the involved site was completed. The patient subsequently had widespread tumor recurrence, including bony metastases. A regimen of monthly pamidronate infusions and thalidomide was commenced. She died of metastatic disease 16 months after transplantation.

Case 4

A 45-year-old previously healthy man had dyspnea on exertion and was found to have a large tumor in the left atrium. He underwent incomplete resection of the tumor, which showed gross invasion of the left pulmonary vein. Pathologic examination revealed high-grade intimal cell sarcoma. The patient received 4 cycles of doxorubicin and ifosfamide chemotherapy after the operation. Preoperative scans showed no signs of metastatic disease. The patient was referred for heart-lung transplantation, which he underwent 2 months after listing. The postoperative course was complicated by severe reperfusion lung injury and pneumonia. He was eventually discharged on the 65th postoperative day. He was readmitted 6 weeks later with symptoms of dyspnea and headache and was found to have diffuse pneumonitis and a large right parietal mass. Right craniotomy was performed and showed high-

grade spindle cell sarcoma identical to the cardiac tumor. After craniotomy, progressive respiratory failure requiring tracheostomy developed. The patient died of respiratory failure 5 months after transplantation. Postmortem examination revealed diffuse pneumonitis, alveolar damage, and moderately severe bronchiolitis obliterans.

Discussion

The 4 case studies presented here indicate that orthotopic heart-lung transplantation for highly selected patients with primary cardiac sarcoma is technically feasible. All the patients had either initially unresectable tumors or persistent disease after failed attempts at complete resection. To be considered for transplantation, patients underwent an extensive workup for metastatic disease. Nevertheless, in 1 case the symptoms heralding the development of cerebral metastases only became apparent the day before transplantation, and results of magnetic resonance imaging of the brain from another institution were not available until after the surgery. All 4 patients had doxorubicin and ifosfamide-containing regimens before transplantation. All had margins free of tumor at resection-transplantation.

Despite this dual modality approach, all patients had progression of disease, at median intervals of 12 months (range 10-40 months) and 5 months (range 0-34 months) after diagnosis and transplantation, respectively. Progression of disease comprised local recurrence in the chest in 1 case, cerebral metastases in 2 cases, and mesenteric recurrence in 1 case. Three of 4 patients have died. Median survivals from diagnosis and transplantation were 39 months (range 11-57 months) and 31 months (range 5-49 months), respectively. Two patients had bronchiolitis obliterans develop after transplantation. There were no episodes of acute graft rejection.

Primary cardiac sarcoma is the second most common type of primary cardiac tumor, with myxoma having the highest incidence.²⁰ Historically, long-term survival of patients with primary cardiac sarcoma has been poor, with complete surgical excision often not feasible^{5,7,8} and no clearly beneficial role for chemotherapy and radiotherapy.⁵ Previous anecdotal reports of cardiac transplantation, often as a therapeutic last resort, have been variable, with both good outcomes with follow-up of between 8 months and 5.5 years^{11,12,14,18,20} and poor survivals of between 2 and 9 months.^{16,17} To our knowledge, this is the first reported series of cases of combined heart-lung transplantation for primary cardiac sarcoma. Our experience with these 4 cases is similar to that seen with cardiac transplantation alone, with only 1 surviving patient with cerebral metastases at 4.1 years after transplantation.

All patients in this series received doxorubicin-containing chemotherapy before transplantation. Questions remain as to the optimal chemotherapy agents (if such agents exist at all), the number of chemotherapy cycles that should be

recommended before transplantation, and whether additional chemotherapy should be administered after transplantation to attempt to control metastatic spread of the disease. Authors of other series of cardiac transplants^{12,13,14,16} claim that chemotherapy must be an integral part of the treatment, but the evidence to support this is not convincing. Despite chemotherapy, patients with cardiac sarcoma in these series died of distant metastatic disease.

The role of transplantation in the treatment of a patient with a history of cancer remains controversial. One concern has been the potential for the risk of neoplasia to be increased after transplantation by immunosuppressive therapy. There does appear to be an increased incidence of new tumors, in particular non-Hodgkin lymphoma and skin carcinomas, after transplantation. In a study from the University of Pittsburgh, the incidence of lymphoma was 2.3% in cardiac allograft recipients, with a 3.8% incidence in recipients of combined heart and lung transplants,²¹ but the incidence has been reported as high as 13% in heart recipients and 33% in heart-lung recipients.^{22,23} The incidence of skin cancer, especially squamous cell carcinoma, is also increased, with skin cancer occurring in 10.7% of recipients of cardiothoracic transplants in an Australian study.²⁴ An increased incidence of sarcomas (excluding Kaposi sarcoma) is also observed in transplant recipients relative to the general population (1.8% vs 0.5%).²⁵ The risk of recurrent tumor in a patient with a known diagnosis of cancer, not primary in the heart, after transplantation does not appear to be increased.^{18,26} In those cases the tumor cells do not have direct access to the systemic circulation but must pass through the lungs. There was a 100% survival rate after heart transplantation in a series of 11 patients with malignant disease with no evidence of recurrent or metastatic tumor.¹⁸ One of these patients had a cardiac angiosarcoma, but the follow-up was short at 8 months. Two patients had previous therapy and were disease free; 1 had had Ewing sarcoma and the other had had osteogenic sarcoma. Follow-ups for these three patients were 9 months, 6 months, and 3 years 5 months, respectively. In the other study, 7 patients with preexisting malignancies underwent cardiac transplantation, with a 2-year survival of 100%, and at an average follow up of 31 months only 1 patient has a recurrent basal cell carcinoma.²⁶ None of these patients had a history of sarcoma.

In conclusion, our limited experience with combined heart and lung orthotopic transplantation as an aggressive approach to the treatment of highly selected patients with primary cardiac sarcomas is disappointing. The future role of transplantation for patients with such high metastatic potential remains unclear. All patients in our series had metastatic disease develop, and this remains the major obstacle to the utility of this therapeutic intervention.

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