

Is Heart Transplantation for Primary Cardiac Sarcoma a Useful Therapeutic Option?

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Primary cardiac sarcomas are rapidly progressive malignant tumors. No good therapeutic option is known. In recent years, heart transplantation has sometimes been performed in selected patients with cardiac sarcoma.

We retrospectively analyzed 8 patients with primary cardiac sarcoma referred to our center to undergo assessment for heart transplantation. After an exhaustive study of the extension of the tumor, 6 patients were added to the waiting list for heart transplantation. Heart transplantation was not performed in 3 of these patients due to evidence of extracardiac extension, but the procedure was completed in the remaining 3 patients. The median survival in «intention-to-treat» analysis (transplantation or a frustrated transplantation attempt) was 8.5 months. Overall, the median survival of the 3 patients who underwent transplantation (12 months) was similar to that of the 5 patients who did not (11 months).

Key words: Heart transplantation. Primary cardiac sarcoma. Heart neoplasm.

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¿Es útil el trasplante cardíaco como tratamiento del sarcoma cardíaco primario?

El sarcoma cardíaco primario es un tumor maligno de evolución rápida y fatal. Se desconoce en la actualidad cuál debe ser la aproximación terapéutica ideal a esta enfermedad. El trasplante cardíaco se ha utilizado ocasionalmente como tratamiento definitivo de esta entidad.

Presentamos a 8 pacientes diagnosticados de sarcoma cardíaco primario que fueron valorados para trasplante. Después del estudio de extensión, 6 pacientes fueron incluidos en lista de espera para trasplante cardíaco. En 3 pacientes, la intervención no se pudo completar al demostrarse intraoperatoriamente la extensión extracardíaca del sarcoma, y en tres pacientes el procedimiento se llevó a término. La mediana de supervivencia por intención de tratar (trasplante o intento de trasplante) fue de 8,5 meses. La mediana de supervivencia de los 3 pacientes trasplantados (12 meses) fue similar a la de los 5 pacientes no trasplantados (11 meses).

Palabras clave: Trasplante cardíaco. Sarcoma primario cardíaco. Neoplasia cardíaca.

INTRODUCTION

The incidence of primary cardiac neoplasia is low, with rates described as being between 0.001% and 0.03%.¹ The majority of these tumors are benign or of a low level of malignancy. Nevertheless, up to 25% of cardiac tumors are malignant,² with sarcomas occurring most frequently.

Orthotopic cardiac transplant has surfaced as a treatment alternative for these patients given the poor results of conventional treatment.

We present a series of patients diagnosed with primary cardiac sarcoma (PCS) who were evaluated for cardiac transplant as a therapeutic option for their disease.

RESULTS

We evaluated 8 patients with a diagnosis of PCS for possible inclusion in the cardiac transplant program. Demographic and clinical data are shown in Table 1.

After an initial extension study, we excluded 2 patients due to extracardiac tumor extension (1 patient with extension to the inferior vena cava and the other to the pulmonary veins). The rest of the patients were placed on the cardiac transplant waiting list. Together with the oncology department, we decided to administer chemotherapy prior to cardiac transplant. One patient who was transplanted at 8 days did not receive

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TABLE 1. Demographic and clinical data on the 8 Patients in our series

Mean age, years	36±14.1	
Sex, M/F	4/4	
Symptomatology		
Pericardial hemorrhage	4 (50%)	
Pericarditis	3 (37.6%)	
Tamponade	3 (37.6%)	
HF, right or left	4 (50%)	
Constitutional syndrome	2 (25%)	
Mean delay before diagnosis, months	4.5±2.1	
Tumor origin, right/left	6/2	
Pathological anatomy		
Angiosarcoma	5 (62.5%)	
Pleomorphic sarcoma	1 (12.5%)	
Rabdomiosarcoma	1 (12.5%)	
Malign fibrous histiocytoma	1 (12.5%)	
Anatomopathological diagnosis	Attempt	Diagnosis
Pericardiocentesis	4	0
Thoracotomy biopsy	8	8
Extension study		
TTE	100%	
TEE	100%	
Thoracoabdominal TAC	100%	
MRI	67%	
Cavography	83%	
Gallium gammagraphy	83%	

HF indicates heart failure; TTE, transthoracic echocardiogram; TEE, transesophageal echocardiogram; MRI, thoracic magnetic resonance imaging with gadolinium.

chemotherapy. The average length of time from the diagnosis of the tumor to the transplant or attempted transplant was 52 days (range 10 to 90 days). The average length of time from inclusion on the waiting list until transplant was 34 days (range 8 to 48 days). Table 2 shows the surgical results.

In 3 of the 6 cases we were unable to complete the transplant due to obvious extracardiac involvement following thoracotomy. In patient number 1 there was infiltration of the right wall pleura. In patient number 2, the inferior vena cava had been infiltrated, and there were no possible resection margins for the performance of graft anastomosis, and in patient number 6 there was involvement of the pulmonary veins and mediastinum. All cardiac anastomoses were performed

using conventional techniques (native atrium to donor atrium) with broad atrial resection and histological verification of the free margins of the tumor via intraoperative biopsy.

Patient number 5, transplanted due to a rabdomiosarcoma originating in the left ventricle, survived 28 months until the appearance of a new local relapse in the native atrium. After a new extension study, we decided to perform a cardiac re-transplant. Seven months later the patient had another relapse in the left atrium and veins, resulting in the patient's death 1 month later.

The remainder of the patients in whom we attempted cardiac transplant died due to remote spread of the tumor.

The 2 patients who were not included on the cardiac transplant waiting list due to evidence of extracardiac involvement survived after diagnosis for 11 and 18 months, respectively. Death was due to cerebral metastasis in one patient and for contiguous hepatic involvement in the other. Treatment of both patients consisted of tumor resection and chemotherapy.

Figure 1 shows the actual survival rates of the 6 patients in whom we attempted treatment. The average survival rate was 8.5 months (range 1 to 36 months). The transplanted patients were treated with double immunodepressive therapy while chemotherapy was taking place (cyclosporine and prednisone).

DISCUSSION

Cardiac sarcomas are very aggressive tumors. In fact, 80% of patients have metastatic disease at the time of diagnosis, and 90% survive less than 9 months following diagnosis.^{3,4} The aggression of these tumors in many cases limits conventional surgical resection, which in some series was only used in 15% of cases,³ without providing an improvement in prognosis. Chemotherapy and radiotherapy do not offer better prospects.⁵ Given all this information, cardiac transplant has been proposed as a therapeutic option for these patients.⁶

Less than 30 of the cardiac transplant series published in the literature are for the treatment of primary cardiac tumors (25% are for benign non-resectable tu-

TABLE 2. Results from transplanted or attempted cardiac transplant patients

1	CTx attempt	1 cycle	6 cycles	30 days	20 days	13 months	Cerebral metastasis
2	CTx attempt	No	No	10 days	8 days	8 months	Pulmonary metastasis
3	CTx	4 cycles	6 cycles	90 days	45 days	12 months	Cerebral metastasis
4	CTx	1 cycle	No	45 days	33 days	9 months	Cerebral metastasis
5	CTx	1 cycle	5 cycles	60 days	35 days	36 months*	VVPP relapse
6	CTx attempt	4 cycles	No	90 days	48 days	1 month	Cerebral metastasis

*Patient with cardiac re-transplant (see text). CTx indicates cardiac transplant; CT, chemotherapy; DX, diagnosis; VVPP, pulmonary veins.

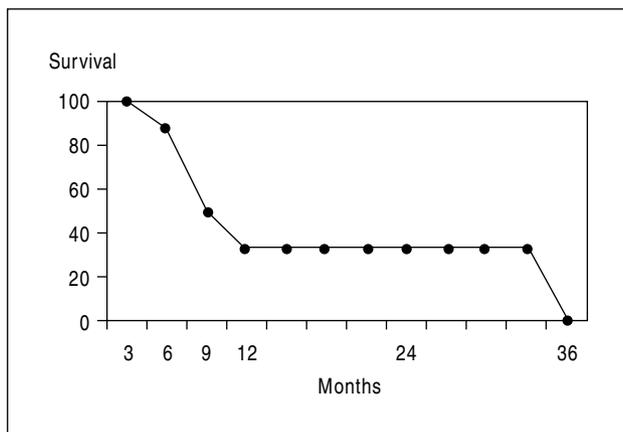


Fig. 1. Actual survival by transplant attempt.

mors and 75% for malignant tumors). The cardiac tumor for which cardiac transplant is most frequently used is sarcoma.⁷ The mean survival rate for patients transplanted for a benign tumor is reported to be 46 months (range 8 to 105 months), while this number is reduced to 12 months for malignant tumors (range 1 to 36 months).⁷

The principal problem with cardiac transplant in these patients is the need to confirm the absence of extracardiac tumor extension. In the majority of cases, studies were performed with echocardiogram and thoracoabdominal and cranial computed tomography. For some years cardiac magnetic resonance imaging has been used with the aim of characterizing intracardiac mass, and its relationship to neighboring structures with or without the administration of gadolinium.⁹ In spite of using this technique in the greater part of our patients, we were not able to reliably determine the involvement of neighboring structures. Recently, positron emission tomography (PET) has begun to be used for the study of cardiac tumors.¹⁰ Future studies in this field, although new, will help clarify the sensitivity of PET for the delimitation of tumor extension.

As can be seen in Table 1, our group performed a more exhaustive extension study than those performed by the majority of transplant groups. In spite of being on the transplant list a relatively short period of time (average 34 days), we found extracardiac involvement upon attempting cardiac transplant in 50% of patients. This finding necessitated the use of a graft in a second receptor prepared for this eventuality, following the course recommended by the majority of the transplant groups who advise having a second receptor prepared.^{7,9} We believe that diagnostic techniques do not exist at the present time that are efficient enough to discriminate with certainty those patients who are not candidates for cardiac transplant from those who are, thereby avoiding the risks involved in a thoracotomy.

As in our series, the majority of deaths in patients

transplanted secondary to PCS reported in the literature are due to metastatic disease.⁹ The role immunodepressive drugs may play in the early appearance of relapses is unknown. For this reason, Baay et al¹¹ carried out a cardiac transplant on a patient with angiosarcoma who had received chemotherapy and radiotherapy pre-operatively and chemotherapy post-operatively, and they achieved survival of the patient for at least 33 months. This strategy has been adopted by the majority of authors.^{7,9} Our group systematically followed this approach, but without being able to reproduce their good results.

A controversial theme is what type of surgery or graft anastomosis should be performed on these patients. The majority of authors recommend using the Dreyfus technique,¹² in which both atria are resected and the venas cava and pulmonary veins are anastomosed to a left atrial cap. Although a large portion of surgical groups has used this approach,¹³⁻¹⁵ other authors performed a broad surgical atrial resection with histological proof of borders free of disease and conventional anastomosis.^{7,16,17} This was the surgical technique that we used for 3 transplants. Given that reported experience with these types of tumors is scarce, it is difficult to define what may be the best approach.

Michler and Goldstein⁹ reported one of the best series described of cardiac transplant secondary to cardiac tumor. They performed cardiac transplant in 6 patients (2 fibromas, 1 feochromocytoma, and 3 different types of sarcomas). In these last 3 patients they described survival rates at the time of publication of 6 and 34 months in 2 patients. The third patient died of unknown causes less than 3 months post-transplant. In another series of 6 patients,⁷ 5 of whom underwent transplant for PCS, the average survival rate was 11.5 months (range 3 to 36 months).

In a recent review by Rodríguez et al,¹⁸ actuarial survival rates with cardiac transplant were reported of 54% and 45% at 12 and 24 months, respectively, which is very similar to survival rates with conventional treatment. Our analysis of attempt to treat is more discouraging than that of these authors, with survival rates of 33% and 16% at 12 and 24 months. The average survival rate of the transplant group (12 months) is similar to that of the non-transplant group (patients in whom transplant was attempted or patients not included on the waiting list), which was 11 months.

Analyzing the data from the 28 patients transplanted due to primary cardiac tumor (7 benign and 21 malignant) in the review by Gowdamarajan et al,⁷ we found that 7 of the 21 transplanted patients had a mean survival rate of 27 months (range 6 to 66 months) and were, up to the time of publication of the review, without evidence of disease relapse, so that this therapeutic option should not be systematically underestimated. Nevertheless, only 1 of these 7 patients with a better survival rate presented with angiosarcoma, which is

the most frequently-occurring type of sarcoma, most often results in transplant, and which has the worst prognosis. The same finding appears to be confirmed by our experience, in which the average survival rate for patients with angiosarcoma was 9 months, while that of patients with other types of tumors reached 18 months. All this data appears to indicate that the histological type of tumor may be a very important factor when deciding whether or not to perform a cardiac transplant; the existence of an angiosarcoma would be a contraindication, while in other less aggressive sarcomas cardiac transplant may be a reasonable option. Recently a case of rhabdomyosarcoma has been published with a post cardiac transplant survival rate of 102 months, confirming the above.¹⁹

CONCLUSIONS

In our experience and in accordance with the widespread unfavorable data, we believe that cardiac transplant as treatment of PCS does not offer any advantages over conventional treatment. Cardiac transplant must only be considered in highly selected patients with different histological types of tumor than angiosarcoma. Actual diagnostic means available to us to determine extracardiac involvement are not sufficient to exclude this possibility, and if we decide on the transplant option there must always be a second receptor ready. The benefit of chemotherapy prior to and following the transplant is not clear, so that this strategy should be followed with caution given the possibility of side effects and interaction with medications given to the transplant patient.

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