Cardiac Transplantation and Neoplasms: Experiences at Escola Paulista de Medicina of the Federal University of São Paulo

Walter Teixeira de Mello Junior, João Nelson R. Branco, Roberto Catani, Luciano de Figueiredo Aguiar, Rodrigo Pereira Paez, Enio Buffolo
Universidade Federal de São Paulo - São Paulo, SP - Brazil

Objective

To study the occurrence and types of neoplasms developed by patients who underwent an orthotopic cardiac transplantation under the Program of Cardiac Transplantation of Escola Paulista de Medicina, Federal University of São Paulo.

Methods

This is an observational study of 106 patients who underwent orthotopic cardiac transplantation from November 1986 to September 2002 and survived at least thirty days following the procedure. The triple immunosuppressive regimen given included cyclosporin A, azathioprine and a corticosteroid agent. Only two patients received OKT3 in addition to the regimen established. Mean follow-up was 61.4 months (ranging from two months to 192 months).

Results

Twenty-three patients (21.3%) developed neoplasms – 56.5% of these were skin neoplasm, 30.1%, solid tumors, and 13.4% of post-transplant lymphoproliferative disease (PTLD). Mean interval between transplantation and diagnosis of neoplasm was: 54.9 months for skin neoplasm; 24.8 months for solid tumors and 70.3 months for PTLD.

Conclusion

Malignant neoplasms are relatively common in the population studied. Skin cancer was the most common type compared to the other types of neoplasms. Solid tumors were more frequently diagnosed than the lymphoproliferative diseases in the population examined.

Key words

cardiac transplantation, neoplasms, surgery

Mailing Address: Walter Teixeira de Mello Junior • Rua Napoleão de Barros, 715, 3º andar - 04023-062 – São Paulo, SP - Brazil
E-mail: cardiovascular.dcir@epm.br
Received on 08/11/04 • Accepted on 07/01/05

Heart surgery centers have progressively included orthotopic heart transplantation in their activities as a therapeutical option for managing patients with end-stage cardiac diseases. Advances in surgical and in myocardial preservation techniques, severe selection of receptors, major progress in rejection control and ability to prevent and to treat several types of infections contributed to increase the survival of organ recipients[1,2]. In spite of this progress, the occurrence of late complications such as graft vascular disease and neoplasm affect the survival of these patients.

One of the first studies linking neoplasms, transplantation and immunosuppression was published by Penn et al in 1969[3]. Later several papers confirmed the increase of the incidence of neoplasms in individuals who underwent transplantation[4-9]. If on the one hand the pharmacological advances in immunosuppressive therapy ensured a more effective control of acute rejection and increased the survival of patients in the short term, on the other the incidence of certain types of neoplasms is one of the main limiting factors in the long term for these patients[2,10].

Patients who have undergone transplantation present a three to four-fold increased risk of developing a neoplasm compared to the general population; however this risk can be higher than a hundred-fold for certain types of neoplasms[2,7]. Mean length of time for post-transplant neoplasm to arise ranges from twelve to eighteen months. The estimate incidence of this type of disease is 1%-2% per year[1]. Skin and lip tumors are the most common in patients who undergo transplantation. However the incidence of many of the malignant neoplasms found in the general population (lungs, prostate, breast and colon) is not increased in the transplant population submitted to immunosuppression[2].

Some tumors that are rarely observed in the general population are more common in patients who underwent transplantation, including non-Hodgkin lymphomas and lymphoproliferative disorders, currently gathered under the term Post-transplant lymphoproliferative Disorders (PTLD). The origin of PTLD is unclear but it is believed that it may depend on the monoclonal or polyclonal proliferation of B-lymphocytes infected with the Epstein-Barr virus. In addition to the neoplasms already mentioned, other types such as Kaposi's sarcoma, renal carcinomas, *in situ* carcinoma of the cervix, hepatobiliary carcinomas, anogenital carcinomas and other sarcomas.

Skin and lip tumors in patients who undergo transplantation present some features that are rarely observed in the general population such as higher rate of squamous cell carcinomas compared to basal cell carcinomas[11]. Other unusual characteristics are the presence of tumors in several sites, frequent association with Kaposi's sarcoma and increased incidence in younger patients[12,13]. Presence of anogenital neoplasms in patients younger than the general population is also observed[2]. In regard to PTLD, associations with the Epstein-Barr virus were observed: involvement of extranodal sites and marked preference for the brain and the transplanted organ[12-17].

Methods

An observational descriptive study of 129 patients who underwent orthotopic heart transplantation from November 1986 to September 2002 under the Heart Transplantation Program of Cardiovascular Surgery at the Escola Paulista de Medicina of the Federal University of São Paulo was conducted. Twenty-three patients out of the 129 died from different causes within a month following surgery and were therefore excluded from the study. The sample consisted of 106 patients: 87 men and 19 women. At the time of transplantation the mean age was 43.7 years (ranging from 12 to 64 years).

Transplantation was indicated to treat the following heart conditions at their end-stage: idiopathic dilated cardiomyopathy: 44 patients (41.5%); Chagas' cardiomyopathy: 31 patients (29.2%); ischemic cardiomyopathy: 23 patients (21.6%), peripartum cardiomyopathy: three patients (2.8%), other cardiomyopathies: five (4.7%) (a hypertrophic, a congenital, a valvular, a viral and a post-radiotherapy cardiomyopathies). Significant history of smoking was present in five patients. All patients were submitted to immunosuppressive therapy with cyclosporine A, azathioprine and a cortiscosteroid agent. During that period, two patients also received orthoclone (OKT3) for treating rejection. Mean follow-up after the transplantation was 62.5 months (ranging from 2 to 192 months).

Immunosuppressive therapy - The protocol of the immunosuppressive regimen consisted of cyclosporine A, azathioprine and corticosteroid as shown in Table 1.

Observations: The use of prednisone was discontinued at the second or third postoperative month in patients with Chagas' disease or in those who developed diabetes or psychoses as complications because of the use of prednisone; Induction therapy was not applied; only two patients received OKT3 for treating episodes of rejection; episodes of moderate/severe rejection were treated with methylprednisone 1 g IV/day for three days followed by prednisone 0.5 – 1 mg/day until the biopsy revealed normal results.

Monitoring rejection - Patients were routinely submitted to endomyocardial biopsies performed based on the following schedule: once a week in the first month; once a fortnight in the second month; once a month for the next four months, and every two months during the first year. Additional biopsies were performed when

clinical changes or findings suggested organ rejection according to objective procedures (physical examination, electrocardiogram and echocardiogram)

Results

Characteristics of the patients - The clinical profile of patients who developed neoplasms is shown in Table 2.

Twenty-three patients out of the 106 (21.6%) studied developed neoplasms. Mean follow-up of these 23 patients was 73.1 months (ranging from 11 to 192 months).

Mean age of patients at the time of transplantation was 52.04 years (ranging from 29 to 62 years). Out of the patients who developed cancer, 22 were male (95.6%) and only one patient (4.4%) was a female. Patients who developed neoplasms had undergone transplantation for treating the following heart conditions: idiopathic dilated cardiomyopathy – 12 patients (52.1%); ischemic cardiomyopathy – 7 patients (30.4%); Chagas' cardiomyopathy – 2 patients (8.6%); post-radiotherapy

Table 1 – Immunosuppressive Protocol

Drug	Initial Dose	Maintenance Dose
Cyclosporine A	Dose of 4-6 mg/kg body weight/day from the 4th post-operative day on, adjusted based on plasma levels (variation of 200-300 ng/mL in the first three months).	Maintenance of plasma levels between 100-200 ng/mL within the 4th – 8th month and between 100-150 ng/mL in the following months.
Azathioprine	Dose of 2-2.5 mg/kg body weight/day PO preceded by 4 mg/kg body weight in the immediate pre-operative period. Lower dosages in the presence of leukopenia, thrombocytopenia or liver dysfunction	
Methylprednisolone	Dose of 500 mg IV followed by 750 mg – 1 g from the intraoperative period to the third postoperative day.	
Prednisone	Dose of 1-1.5 mg/kg body weight/day PO from the fourth postoperative day on.	Minimum dose of 10 mg/day at the six-month follow-up and minimum daily dose or no drug one year following surgery.

Table 2 – Clinical profile of patients who developed cancer

# of the patients	Age (years)	Sex	Cardiomyopathy	Smoking	Disease extension	Time between transplantation/ diagnosis (months)	Histological type	Treatment	Survival following transplantation (months)	Outcome
1	47	M	Dilated	N	Localized	116	Skin BCC	Surgical	192	Alive
2	59	M	Dilated	N	Localized	75	Skin SCC	Surgical	168	Alive
3	54	M	Dilated	N	Localized	24	Skin BCC	Surgical	48	Death
4	55	M	Dilated	N	Localized	48	Skin SCC	Surgical	143	Alive
5	62	M	Dilated	Y	Localized	43	Skin SCC	Surgical	93	Death**
6	55	M	Ischemic	Y	Localized	58	Skin BCC	Surgical	98	Death**
7	49	M	Hypertensive	N	Localized	23	Skin SCC	Surgical	45	Death**
8	56	M	Ischemic	Y	Localized	43	Skin BCC	Surgical	83	Alive
9	50	M	Chagas	N	Localized	55	Skin SCC	Surgical	72	Alive
10	56	M	Dilated	N	Localized	63	Skin BCC	Surgical	72	Alive
11	59	M	Dilated	N	Localized	5	Skin SCC	Surgical	57	Alive
12	48	M	Dilated	N	Localized	89	Skin SCC	Surgical	144	Alive
13	55	M	Ischemic	Y	Localized	60	Skin SCC	Surgical	78	Alive
14	43	M	Dilated	Y	Localized	79	DLPT/CEC	CT	84	Death/Ca
15	60	M	Dilated	Y	Advanced	50	Lung	RT	70	Death/Ca
16	47	M	Ischemic	N	Advanced	17	Prostate Adenoc	Surgical	29	Death/Ca
17	55	M	Ischemic	Y	Advanced	22	Prostate	Surgical	44	Death/Ca
18	60	M	Ischemic	Y	Advanced	19	Adenoc	*	22	Death/Ca
19	56	M	Chagas	N	Advanced	36	SCC/esophagus	RT	38	Death/Ca
20	58	M	Dilated	N	Advanced	9	Adenoc Breast	CT	11	Death/Ca
21	45	M	Dilated	N	Advanced	11	Adenoc	*	11	Death/Ca
22	29	F	Post-partum	N	Localized	75	PTLD	&	75	Death**
23	39	M	Dilated	Y	Localized	39	PTLD	&	57	Death/Ca

** support treatment and diagnosis by necropsia, ** Causes of death other than neoplasms. BCC– basal cell carcinoma; SCC– squamous cell carcinoma; Adenoc – adenocarcinoma; RT– radiotherapy; CT– chemotherapy*

cardiomyopathy: 1 patient (4.3%) and hypertrophic cardiomyopathy: 1 patient (4.3%). Mean time between transplantations and detection of the neoplasm was 44.9 months (ranging from two to 116 months).

Table 3 shows the distribution of frequencies and types of câncer found.

Table 3 – Distribution of frequencies according to types of cancer

Neoplasm		Histological type	# of cases	%
Skin		Squamous cell carcinoma	8	34.80%
		Basal cell carcinoma	5	21.70%
Solid Tumors	Prostate	Adenocarcinoma	2	8.60%
	Lung	Squamous cell carcinoma	1	4.30%
	Breast	Adenocarcinoma	1	4.30%
	Esophagus	Squamous cell carcinoma	1	4.30%
	Adenocarcinomas *		2	8.60%
PTPD			3	13.40%
Total			23	100%

** The primary sites of metastatic adenocarcinoma of two patients remained unknown*

Patients' survival - Survival of heart transplant patients is examined based on the survival function provided by the Kaplan-Meier analysis. Figure 1 shows survival of patients with "no neoplasm", with "skin neoplasm" and with "other types of neoplasms" (solid tumors and PTLD). The figure also shows that the likelihood of survival is higher for those with "skin neoplasm" and "no cancer" than for those with "other types of neoplasms".

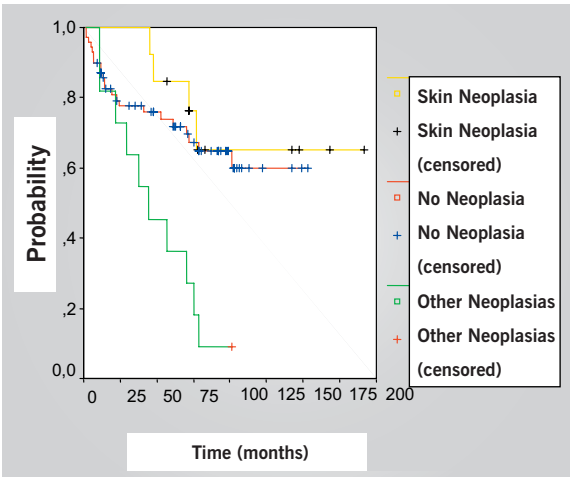

***Fig. 1** – Kaplan-Meier Survival Function*

Point and interval estimates of mean survival (in months) after heart transplantation applying the Kaplan-Meier analysis are shown in Table 4. Estimate mean survival of subjects with "other types of neoplasms" presents an important difference compared to subjects with "no neoplasm" and "skin neoplasm".

Table 4 - Statistics for length of survival following heart transplantation

Factors	Mean	Confidence Interval (95%)	
	(months)	Lower limit	Upper limit
With other types of neoplasm	48.82	31.96	65.67
No neoplasm	107.37	91.84	122.90
With skin neoplasm	146.95	110.57	183.33

Discussion

According to the literature, the incidence of malignant neoplasms is approximately 1-2% a year in patients who undergo heart transplantation. Skin tumors are the most frequent type observed in organ transplant recipients and include squamous cell carcinomas, basal cell carcinomas, melanomas and Merkel's cell carcinoma[19-22]. Post-transplant lymphoproliferative diseases (PTLD) ranks second.

Solid tumors ranks third following those two types of tumors that make up most of de novo malignant tumors observed in organ transplant recipients. Solid tumor cancers are classified in two groups: those whose incidence is similar to that found in comparable groups from the general population – they include lung carcinoma, breast carcinoma, prostate cancer and brain cancer – and those whose incidence in organ transplant recipients is higher – they include renal cancer (in renal transplant recipients) and genital cancer in women who present uterine cervix carcinomas, perianal/anal carcinomas and vulvar carcinomas[2]. Recent statistical data show that colon carcinoma has a higher incidence in transplant recipients than in the general population[29] and that cancer of the ovary is the only neoplasm with lower incidence in the population of transplant patients compared to the general population [30-33].

The incidence of malignant cancer in this small sample of 106 patients submitted to heart transplantation was 1.35% per year. Nonmelanoma skin carcinoma was the most common type. It was observed in 56.5% of the subjects with neoplasms, in accordance to rates described by the international literature. Excessive sun exposure is a risk factor for developing skin cancer as shown by several studies that indicate an increased risk of approximately 21 fold in areas overexposed to sunlight[12.16.17.21-23]. The frequency observed in this sample may be related to climate conditions in Brazil, where most of the days are sunny. Actually, statistical data from the Ministy of Health show that the incidence of skin cancer is the highest amongst different types of tumor in this country and the estimate risk for developing it in 2005 is 62 cases for each 100,000 men and 60 for each 100,000 women[33].

Post-transplant lymphoproliferative diseases, PTLD, represent the second most common type of neoplasm

developed by transplant recipients[34-36]. Most cases of PTLD develop within the first year post-transplant and it seems to be related to the Epstein-Barr virus (EBV). A minority of patients with EBV-negative PTLD present the same distribution over a period of ten years after transplantation[37-40]. There may be a predominance of T or B cells with monomorphic or polymorphic standard in PTLD [36]. The most benign form often incidentally found in transplant pediatric recipients is hyperplasia of the tonsils. PTLD can develop in single or multiple anatomical sites. It may involve solid organs or lymphonodes or it may histologically vary from hyperplasic lesions to lymphomas[36,41-44].

Some factors associated with better prognosis are: to be younger at the time that the disease arises; to be located in a single anatomical site; involvement limited to the graft and to be a patient who may have the doses of immunosuppressive agents reduced[45]. On the other hand, involvement of the central nervous system is related to a poorer prognosis[46,47]. Some studies show that patients with EBV-negative neoplasm that received OKT3 as induction immunosuppressive therapy may present a higher risk for developing PTPD[45,48,49].

In this study, three patients developed PTPD (13.04% of all types of neoplasm diagnosed). One of them eventually died because of other complications (acute rejection, infection by *P carinii*, and disseminated intravascular coagulation). PTLD had affected his mediastin and he also presented reactional hyperplasia with expression of the Epstein-Barr virus and infiltration of atypical lymphomononuclear cells in the splenic parenchyma.

The necropsy of another patient who eventually died while studies were being performed to reach a diagnosis confirmed PTPD. It also showed liver involvement and the Epstein-Barr virus infection. The biopsy of a third patient revealed a comprehensive infiltration of the anorectal mucosa, histopathological and immunohistochemical studies resulted in diagnosis of PTLD with pattern of polymorphic B-cell lymphoma. The neoplasm was also EBV-positive.

Solid tumors were more commonly found than PTLD and represented 30.1% of the neoplasms diagnosed. The seven types of neoplasm developed by this population submitted to cardiac transplantation were: prostate adenocarcinoma: 02 patients, lung squamous cell carcinoma: 01 patient, breast adenocarcinoma: 01 patient, esophagus carcinoma: 01 patient and disseminated metastatic neoplasm (adenocarcinoma) with unknown primary site: 02 patients. Relevant facts observed in patients with prostate cancer were the relative early development of the disease after the transplantation (mean interval of 19.5 months), mean age (52 years) below that presented by subjects in the general population that develop cancer (72 years) [26] and short survival after diagnosis (mean of 36.5 months).

Prostate cancer is the second most common neoplasm in men from the general population and the third in the population submitted to transplantation. At the time of diagnosis, lung and esophagus carcinomas were in advanced stage. In transplant patients, lung cancer is biologically aggressive – it presents early metastatic dissemination and results in advanced stage at the time of diagnosis[5,9,24]. Breast cancer, similarly to what is observed regarding neoplasms in transplant recipients, affects these patients at age below to that presented by the general population for the same disease and is more aggressive. Furthermore, a higher percentage of men with breast cancer has been identified in the transplant recipients compared to its incidence in the general population[50,51].

It is common to have transplant candidates with previous history of breast cancer or active breast cancer[52,53]. A recent study examined possible transplant recipients who had had breast cancer and that had been submitted to appropriate interventions with intention to cure based on tumor staging[53]. All patients had to wait five years or more before transplantation. The recurrence rate for patients with stage I or II neoplasms ranged from 5 to 8% but it increased to 64% in patients with stage III disease[53]. Results of that study suggest that in the presence of stage III breast cancer or further there is absolute contraindication for transplantation whereas patients with previous history of stage I or II breast cancer submitted to adequate curative treatment and prolonged transplant waiting time can be transplant candidates.

In our study there was a male patient with breast adenocarcinoma with previous history of breast cancer that had been treated with surgery associated with radiotherapy. The neoplasm was considered cured and the heart transplantation was indicated for treating an end-stage post-radiotherapy cardiomyopathy. Nine months after the transplant we observed a recurrence of the breast tumor. All patients who developed tumors in solid organs died because of the neoplasm.

Worth of mention is a study carried out by Brazilian researchers that examined the incidence and the characteristics of neoplasms following a heart transplantation for treating chronic Chagas' disease compared to heart transplantation for treating other cardiomyopathies[54]. Ninety-one patients were studied and 16 presented Chagas' cardiomyopathy. Six out of the 16 patients (37.5%) developed malignant neoplasms (post-transplant lymphoproliferative disease: 03 patients, Kaposi's sarcoma: two patients, squamous cell carcinoma: 01 patient) detected during post-transplant clinical follow-up that lasted 25.3 ± 2.1 months compared to two out of the 75 patients (2.7%) from the group that presented cardiomyopathy non-related to Chagas' disease. These latter ones presented neoplasms (post-transplant lymphoproliferative disease and a schwannoma affecting the skin) during a 34.6 ± 3.6 months of clinical post-transplant follow-up. The study concludes that the incidence of malignant neoplasms is higher in patients with Chagas' cardiomyopathy submitted to cardiac transplantation.

In our study, chronic Chagas' cardiomyopathy was the reason for indication of heart transplant in 31 patients (29.2% or 31 out of 106 patients). Only two out of the 31 (6.4%) developed a neoplasm (skin cancer and esophagus cancer).

A consensus for surveillance of neoplasms in transplant recipients was recently published at the *American Journal of Transplantation*[54]. Recommendations include annual chest x-ray, Pap smear for women over the age of eighteen years for detecting cervical dysplasia or cancer; biennial mammograms beginning at age 40 for high-risk patients and at age 50 for those with lower risk for developing breast cancer, initial colonoscopic examination at age 50 and every five years thereafter or in the presence of symptoms or guaiac-positive stools. All patients with primary sclerosing cholangitis should undergo annual colonoscopy in the presence of chronic intestinal disease. In the presence of intestinal polyposis, recipients should undergo colonoscopy every 6 months until all polyps are cleared, at which point the interval follow-up can be increased. Annual prostate examinations should include digital examination and serum PSA testing. A good physical examination of the body surface to detect the presence of previous or of newly developed skin lesions. Other recommendations can be added such as avoidance of excessive exposure to sunlight, use of sun protection filters and guidelines to perform a self skin examination.

With base on the patients studied, it is concluded that:

The incidence of neoplasms in patients who undergo heart transplantation is high compared to the general population.

Skin neoplasms are the most frequent type found in these patients, differently from what is observed in the general population in which the squamous cell carcinoma is more common.

The incidence of lymphoproliferative diseases in the group studied was not as predominant as reported in the literature.

Differently from skin neoplasms, solid tumors and lymphoproliferative diseases in the population that underwent transplant may be important causes of death in this group of patients.

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