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Original article

Pretransplant malignancy in candidates and posttransplant malignancy in recipients of cardiac transplantation

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Summary

Background: Malignancy is generally considered a contraindication for cardiac transplantation, whereas secondary malignancy has been described under chronic immunosuppression.

Patients and methods: We report here the frequency of malignancy encountered among the 495 patients evaluated at our cardiac transplant centre as well as the incidence and the course of post-transplant malignancy among 129 consecutive patients who underwent cardiac transplantation, with a subsequent minimum follow-up of 6 months.

Results: A total of 10 out of 495 patients (2%) evaluated for heart transplantation presented with a history of previous malignancy: 3 of them underwent transplantation (2 survive, 1 died) whereas in the remaining 7 patients neoplasia was considered a contraindication for cardiac transplantation, and all 7 died (4 cardiac, 3 tumor-related deaths). Post-transplant malignancy was diagnosed in 10 of 129 patients (9%) 35 ± 15 months after transplantation (6 skin cancers, 1 lymphoproliferative disease, 3 solid tumors). No significant association was found between post-transplant malignancy and primary prophylaxis with antithymocyte globulin (ATG) or murine antihuman T-cell monoclonal antibodies (OKT3).

Conclusion: These results confirm that pre-transplant malignancy is not an absolute contraindication for cardiac transplantation and that post-transplant follow-up must include careful monitoring of post-transplant malignancy.

Key words: heart transplantation, malignancy

Introduction

The large increase in successful organ transplantation – including cardiac – during the past 20 years is probably due to the development of new immunosuppressive drugs and the introduction of the triple regimen (cyclosporine, azathioprine, prednisone) in the early 1980s [1]. Early complications include acute allograft rejection, infection and surgical problems, whereas chronic allograft rejection, cyclosporine nephrotoxicity, osteoporosis, accelerated allograft atherosclerosis and malignancies occur in long-term follow-up [1–4]. An increased incidence of neoplastic disorders has been observed in patients undergoing immunosuppressive therapy for organ transplantation [5–12].

Organ allograft transplantation is usually reserved for patients with an end-stage organ disease without evidence of other disease which would jeopardize the result of transplantation. A pre-existing malignancy may carry the risk of recurrent or *de novo* tumors due to therapeutic immunosuppression and possible consequent deficient immunomodulation. However, long-term follow-up in carefully selected groups of patients undergoing orthotopic heart transplantation with pre-transplant neoplastic disease has been described [13–16].

In this study we report the incidence and the outcome of patients presenting with a history of previous malignancy who were referred to our centre for evaluation of cardiac transplantation, as well as the incidence and the course of post-transplant malignancy in patients who underwent cardiac transplantation.

Patients and methods

The study includes a retrospective analysis of the incidence of malignancy among 498 patients referred to the cardiac transplant centre of the University Hospital of Zurich between September 1985 and December 1992, as well as the incidence and the course of post-transplant malignancy among the 150 patients undergoing cardiac transplantation during the same period.

Pre-transplant malignancy

For all patients, pretransplant evaluation included along with the usual exclusion criteria (active disease process, extensive degenerative disease, vital organ dysfunction, poor compliance) an extensive diagnostic scrutiny to exclude the subclinical presence of a neoplastic disease by means of clinical, haematological, radiological routine screening including abdominal and pelvic ultrasound. Gastrointestinal endoscopic examination was performed in order to rule out gastrointestinal neoplasia in 118 patients with unexplained anemia and/or guaiacol-positive stool specimens; abdominal and chest CT scans were performed in 31 patients to rule out the possibility of a malignant retroperitoneal or mediastinal neoplastic process.

A history of malignancy was considered primarily a contraindication for cardiac transplantation. However, for selected cases presenting a history of previous malignancy, a further extensive

screening was performed to rule out the presence of any silent disease. In these cases, whether to accept or reject patients for cardiac transplantation was decided on an individual basis by an interdisciplinary panel of specialists (including an oncologist). Particular attention was paid to the natural history of the tumor, the patient's life expectancy under the current optimal treatment of the tumor with regard to the histology, extent of the tumor (involvement of adjacent lymph nodes or anatomical structures) and the tumor-free interval at the time of evaluation for cardiac transplantation.

Post-transplant malignancy

Three patients with heart and lung transplantation were not included. Two patients underwent a second orthotopic heart transplantation; one of them died within a month of acute graft rejection, and the second is alive 55 months after a second heart transplantation. Eighteen patients had survival times of less than 6 months (most of these died because of acute cell rejection, acute infection or immediate post-operative problems). Autopsy was performed in 13 of these 18 patients and no evidence of malignancy was found at necropsy.

Thus, we observed 129 cardiac transplant recipients (118 males, 11 females) with a mean age of 47 ± 11 years (14 to 68 years) and a minimal follow-up and survival time of 6 months. The patient with a second transplantation is included and calculated as one. The mean age of the patients at the time of heart transplantation was 44 ± 12 years, and the mean follow-up was 39 ± 23 months (6 to 99 months).

Immunosuppressive regimen

A total of 33 consecutive patients received early rejection prophylaxis with murine antihuman mature T-cell monoclonal antibodies (OKT3, Cilag) during 14 days at a dose of 5 mg/day intravenously. Ninety-six patients were treated with polyclonal anti-T-lymphocyte-globulin (ATG, Fresenius) over 5 days at a dose of 4 mg/kg/day intravenously. The mean follow-up of patients receiving OKT3 was 41 + 11 months and not statistically different from the follow-up of patients receiving ATG (38 + 19 months) as early rejection prophylaxis.

The total amount administered per patient was 2.7 ± 0–9 g/patient for ATG and 67 ± 14 mg per patient for OKT3; 28 patients received a dosage of OKT3 <75 mg; the mean dosage of OKT3 of the 5 patients receiving > 75 mg was 90 + 8 mg.

All patients received the basic immosuppressive regimen commonly used in our transplantation program which consists of oral steroids (prednisone initially 1 mg/kg/day, tapering after the first week to a mean level of 0.20 + 0.04 mg/kg/day), azathioprine (1.45 + 0.60 mg/kg/day) and cyclosporine (5.2 + 1.5 mg/kg/day).

Episodes of cell rejection were defined according to the classification of the International Society of Heart and Lung Transplantation (ISHT criteria) [17]. Episodes of mild cell rejection (ISHT 3A) were treated with the intravenous application of 1 g methylprednisolone/day for 3 days, episodes with ISHT 3B cell rejection were treated with ATG (5 mg/kg/day) intravenously for 5 days and episodes of recurrent or more severe rejections with OKT3 (5 mg/day) intravenously for 7 days.

Together with the usual monitoring for toxoplasma and cytomegalovirus, posttransplant follow-up included monitoring for the Ebstein Barr Virus (EBV). IgM and IgG antibody levels for EBV were monitored every week during the first month, every month during the first 6 months after transplantation and at every subsequent follow-up control (i.e., 2–3 times/year).

Results

Pre-transplant malignancy

Table 1 shows the 10 patients referred for evaluation for cardiac transplantation presented with a history of malignancy at the time of evaluation. All patients presented with an end-stage cardiac disease (NYHA III or IV) due to dilated cardiomyopathy (4), end-stage coronary artery disease (4), doxorubicin cardiomyopathy (1) and cardiac sarcoma (1).

After evaluation, only 3 patients underwent heart transplantation; in the remaining 7 it was considered contraindicated because of associated neoplastic disease.

Patients with pre-transplant malignancy who underwent cardiac transplantation

- Eight years after successful treatment of a Wilms' tumor including whole abdomen radiation therapy, chemotherapy with vincristine sulphate, dactinomycin, cyclophosphamide and doxorubicin (860/m^2) a 14-year-old patient underwent orthotopic heart transplantation because of an end-stage doxorubicin-induced cardiomyopathy.

Eighty months after successful heart transplantation, the now 22-year-old man is functionally fit and has no signs of tumor relapse or *de novo* neoplasia.

- A 54-year-old man with an end-stage dilated cardiomyopathy was referred for orthotopic heart transplantation. A 4 × 2 × 2 cm polyp of the bulbus duodeni detected during the work-up for transplant evaluation was endoscopically resected. Histological diagnosis revealed a duodenal carcinoid tumor, the immunohistochemical stains demonstrated cells producing secretin, gastrin and somatostatin. The pre-transplant surgical exploration of the abdomen showed one micro-metastasis in the ligamentum hepato-duodenale. The patient underwent heart transplantation after eradication of the semimalignant tumor and confirmation that there was no evidence of tumor relapse. During the 48 months since transplantation, there has been no sign of tumor relapse at the regular endoscopic follow-up nor by gastric hormone evaluation.

- A 31-year-old woman was referred for orthotopic heart transplantation because of a local, echocardiographically detected relapse of a cardiac synovial sarcoma with central necrosis originating from the intra-atrial septum of the right heart. Chest X-ray, pre-transplant chest CT scan and skeletal scintigraphy were negative for extracardiac tumor involvement, and no macroscopic metastasis was detectable at the time of the operation.

Both atria were resected extensively and anastomosis of the pulmonary artery was carried out in a standard end-to-end fashion as distal as possible. No chemotherapy or radiotherapy was administered. Two and a

Table 1. Pretransplant malignancy.

	Age (years)	Sex	Cardiac diagnosis	Severity of cardiac disease (NYHA)	Cardiac history (months)[a]	Tumor diagnosis (tumor treatment)	Severity of tumor disease (tumor extension)	Tumor history (months)[a]	Follow-up (months)[b]
1	51	m	CMP	IV	30	Colon adenocarcinoma (surgery)	C1 (Duke's type)	13	+15 (sudden cardiac death)
2	46	m	CAD	III–IV	15	Lung epithelial cell (surgery, RX)	T2/N1/M0	9	+19 (extensive tumor disease)
3	58	m	CMP	IV	28	Multiple myeloma (CX: alkeran)	stage IIIB (Durie)	43	+12 (sudden cardiac death
4	60	f	CMP	IV	36	Breast adenocarcinoma (surgery, tamoxifen)	T2/N1/M0	15	+12 (sudden cardiac death)
5	43	m	CAD	III–IV	12	Lung small-cell (CX)	T1/N1/M0	9	+6 (sudden death autopsy tumor infiltration)
6	52	m	CAD	IV	28	Lung smooth epithelial (surgery, RX)	T1/N1/M0	14	+7 (diffuse meta)
7	56	f	CAD	III–IV	24	Breast adenocarcinoma (surgery, tamoxifen)	T2/N1/M0	12	+12 (sudden cardiac death)
8	14	m	Doxorubicin CMP	IV	48	Wilms' renal tumor (surgery, RX, CX)	T2/N1/M1	96	Alive, transplanted, 88 (NYHA I)
9	54	m	CMP	III	18	Carcinoid duodenum (surgery)	T1/N1/M0	6	Alive, transplanted, 52 (NYHA I)
10	31	f	Cardiac sarcoma	III	3	Cardiac sarcoma (surgery, HTX)	T2/N1/M0	3	+3 (diffuse mediastinal infiltration)

Abbreviations: CMP – dilated cardiomyopathy; CAD – end stage coronary artery disease; NYHA – New York Heart Assocation classification (I to IV); CX – chemotherapy; RX – radiotherapy; HTX – cardiac transplantation; + – death.

[a] Time interval between tumor diagnosis and the time of evaluation for cardiac transplantation.

[b] Months after the time of evaluation for cardiac transplantation.

half months after transplantation, the patient died of tumor progression with extensive metastasis of the liver and vertebral spine, and compression of the lungs by pericardial lymph nodes. This patient was also included in the group with pre-existing tumors although tumor recurrence in this special case was coincidentally also the main indication for heart transplantation.

Patients in whom pre-transplant malignancy was considered a contraindication for cardiac transplantation (Table 1)

In 7 patients, cardiac transplantation was not performed due to the initial presentation, extent and tumor-free interval at the time of evaluation for transplantation, with respect to the current prognosis of the tumor. There were 1 small-cell and 2 epithelial cell bronchial carcinomas, 2 breast adenocarcinomas, 1 adenocarcinoma of the colon and 1 multiple myeloma. All 7 patients died within 6 to 19 months after transplant evaluation: there were 4 cardiac deaths and 3 deaths associated with extensive progression of the tumor.

However, tumor-free disease was documented in only 1 patient at necropsy.

Post-transplant malignancy

Malignancies developed in 11 of 129 transplant recipients (8.6%); their mean age at the time of transplantation was 50 ± 5 years and 54 ± 4 years at the time of diagnosis of malignant disease. The mean elapsed time before the appearance of malignancy after cardiac transplantation was 35 ± 15 months. The observation period lasted 24 ± 11 months (13 to 44 months) after tumor diagnosis.

For the 11 patients with posttransplant malignancy the mean dosage of cyclosporine, azathioprine and steroids were 5.1 + 0.8 mg/kg/day, 1.43 + 0.5 mg/kg/day and 0.20 + 0.05 mg/kg/day and were not statistically different from the corresponding levels in the 118 patients without evidence of posttransplant malignancy.

Follow-up in patients receiving ATG was 38 + 19 months *versus* 41 + 11 months in patients receiving OKT3 as early rejection prophylaxis. The number of episodes of mild and moderate cell rejection (ISHT > 3a) was 3.2 + 1.7 per patient for the 11 patients with posttransplant malignancy and 3.1 + 1.8 per patient in the group of the 118 patients without evidence of malignancy.

- The most frequent tumors were skin ($n = 6$, 54%): squamous cell carcinoma (3), basal cell carcinoma (2) and malignant melanoma (1), and the mean time to appearance after transplantation was 19 ± 14 months. No local relapse or metastatic tumor progression had occurred after local excision of the tumors at a mean observation time of 34 ± 15 months (14–65 months). Immunosuppression therapy remained the same after total excision of the tumors.

Table 2. Post-transplant malignancy.

Tumour diagnosis	Time of tumor diagnosis (months after HTX)	Early rejection prophylaxis	Tumor treatment	Survival (months after tumor diagnosis)
Squamous cell carcinoma (3 patients)	57/42/9	ATG/ATG/ATG	Excision	52[a]/22[a]/19[a]
Basal cell carcinoma (2 patients)	51/38	ATG/OKT 3	Excision	40[a]/21[a]
Malignant melanoma (1 patient)	50	ATG	Excision, reduced immunosuppression	49[a]
Kaposi's sarcoma (1 patient)	35	OKT 3	Reduced immunosuppression, chlorambucilum	32[a]
Lymphoproliferative disorder (1 patient)	39	OKT 3	Cessation of immunosuppression, chemotherapy	1½[b]
Metastatic adenocarcinoma (stomach)	27	OKT 3	Symptomatic therapy	3[b]
Metastatic adenocarcinoma (colon)	24	ATG	No therapy	1[b]
Breast cancer (T2 N0 M0)	13	ATG	Radical mastectomy	35[a]

[a] Alive after orthotopic heart transplantation (HTX).
[b] Dead.

• There was one case of Kaposi sarcoma occurring 35 months after transplantation and presenting with multiple skin lesions and mucosal involvement of the stomach confirmed at endoscopic and histological examination. Following a drastic reduction in immunosuppression (cessation of azathioprine and reduction in cyclosporine A), there was only partial resolution of the Kaposi sarcoma; complete recovery occurred only after two courses of chlorambucil (5 mg).

• *Lymphoproliferative disease* was diagnosed in one patient who received OKT3 at a dosage of 95 mg 5 months after transplantation and who presented with weight lost, fever of unknown origin and pancytopenia. There was no evidence of recent or acute EBV infection (normal IgM and IgG antibody levels). On bone marrow examination a diffuse lymphoproliferative infiltration corresponding to lymphatic leukaemia or lymphoblastic lymphoma was present. An exact diagnosis of the immunohistological identified T-cells could not be established. Despite cessation of immunosuppressive therapy and chemotherapy with bleomycin, vincristine sulphate, cyclophosphamide, cisplatin and prednisone, the lymphoblastic infiltration of bone marrow persisted.

The patient died one and a half months after tumor diagnosis of a fulminant septicemia induced by agranulocytosis. At necropsy, a persistent bone marrow aplasia without T-cell proliferation, chronic pneumonia and necrotic bronchiolitis caused by an infiltrative aspergillosis were found.

No secondary lymphomas were found in any other long-term surviving patients, particularly in those receiving OKT3 as primary prophylaxis. Secondary lymphomas were not found at autopsy in 13 of the 18 patients who died of rejection or infection during the early follow-up and who were autopsied.

Asymtomatic increase of IgM and IgG antibody levels for EBV occurred in only one patient receiving OKT3 as a primary prophylaxis at 4 and 5 months after transplantation, respectively. There was no evidence of neoplasia or lymphoma in this patient at the three-year follow-up.

• There was one breast adenocarcinoma (T2, N0, M0) occurring 13 months after cardiac transplantation with tumor-free follow-up of 27 months after radical resection and treatment with tamoxifen. Two patients developed gastrointestinal adenocarcinoma at 24 and 27 months after transplantation, both of them with liver metastasis at tumor presentation and a consequent unfavourable course.

Discussion

Our results support the opinion that a history of malignancy is not an absolute contraindication for cardiac transplantation [13–17]. Careful selection of the patients is, however, required with respect to the form of presentation, histology, extent of the tumor, the tumor-free interval at the time of transplant evaluation and the life expectancy under the current optimal treatment of the tumor. Our data also underline the dilemma of this decision and indicate that in patients ultimately not selected for heart transplantation because of a previous history of malignancy more than half died within one and a half years of cardiac causes. However, the growing problem of the shortage of organs due to the imbalance between the increasing number of candidates for cardiac transplantation and the limited number of potential donors with the consequent increasing number of patients dying on the waiting lists suggest that patients with poor tumor-related long-term prognoses should still not be transplanted. The emerging role of the artificial heart in patients with terminal heart diseases remains an experimental procedure in humans but in future could change the perspective of this problem.

In our series, there was only one patient presenting with an history of doxorubicin-induced cardiomyopathy with an excellent cardiac and oncological long-term result. The increasing numbers of patients receiving more aggressive oncological regimens (i.e., those undergoing autologous bone transplantation, for breast cancer or non-Hodgkin's lymphoma) will probably give rise in the future to the problem of cardiac transplantation for selected cases with toxicity-induced cardiomyopathy [18].

Our findings on the incidence and course of post-

transplant malignancy confirm the data of large series and registries indicating malignant skin tumors as the most frequent secondary tumor, with an overall good prognosis [6–12]. In our case of Kaposi sarcoma, a drastic reduction in immunosuppression was not sufficient to obtain a complete resolution and only the addition of chlorambucil resulted in achievement of a definite regression of the Kaposi. One interesting finding in our follow-up study, which included a considerable number of patients receiving OKT3 as early rejection prophylaxis, was the low incidence of lymphoma [19, 20]. This incidence of secondary lymphomas may be explained by the low incidence of EBV infection (<1%) in our patients and by the fact that only a minority of patients received a dosage greater than 75 mg of OKT3. A high prevalence of lymphomas has been reported in patients receiving high dosages of OKT3 [19, 20]. The small number of patients in our series receiving more than 75 mg of OKT3 do not allow a statistical comparison between patients receiving different dosages of OKT3.

Although our findings from a single heart transplant center are based on a retrospective analysis and on a limited number of patients and observation time, and therefore probably underestimate the incidence of post-transplant malignancy, they clearly indicate the importance of pre- and post-transplant tumor screening in patients undergoing evaluation and for patients selected for cardiac transplantation.

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