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Transplantation[®]

BRIEF COMMUNICATIONS

SCREENING FOR SOLID ORGAN MALIGNANCIES PRIOR TO HEART TRANSPLANTATION

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Background. Prognosis of solid organ cancer in immunosuppressed hosts is generally dismal. Therefore, every effort to identify patients with asymptomatic carcinomas before transplantation should be encouraged.

Methods. Sixty-seven patients referred for heart transplantation were examined adhering to the scheme proposed at the 24th Bethesda Conference. To increase the sensitivity of this work-up, the following items were added: tumor marker assays (prostate-specific antigen in males, carcino embryogenic antigen), abdominal ultrasound, CT scan of the abdomen and the thorax, mammography/echography of the breasts, PAP smear, colonoscopy if carcino embryogenic antigen abnormal or occult blood in stool, prostate echography if prostate-specific antigen abnormal or prostate hypertrophy.

Results. Carcinoma was detected in 10 of the 67 patients; for 8 patients of this cancer group, transplantation was denied. Importantly, 9 of the 10 malignancies were detected by means of the diagnostic items that were added to the standard screening protocol. There were no significant differences between the cancer and the non-cancer group regarding mean age, sex, etiology of heart failure, and smoking history. Stratifying patients in younger (i.e., ≤ 54 years) and older (i.e., ≥ 55 years) age groups showed a significantly greater proportion of older patients in the cancer group (8/10=80%) compared to the non-cancer group (25/57=44%), $P=0.04$. After a mean follow-up of 34 months, 5 of the 36 transplanted patients developed a malignancy (4 skin carcinomas, 1 non-Hodgkin lymphoma). There have been no malignancy-related deaths until now.

Conclusion. The importance of a thorough screening program in the triage of candidates with preexisting malignancies, especially in an older patient population, is illustrated in this report.

INTRODUCTION

Heart transplantation has become an accepted and highly successful therapy for end-stage cardiac failure. The lack of suitable donor hearts is emphasized by an unrelentingly increasing pool of heart failure patients and hence an unacceptable mortality rate on waiting lists. It is therefore mandatory for transplant programs to insist on a severe and thorough screening of possible recipients to ensure optimal morbidity and mortality after transplantation.

Long-term survival after heart transplantation is determined by allograft vasculopathy and the emergence of malignant diseases. Although difficult to prove, it is likely that at least part of these carcinomas are present before transplantation, and would perhaps be detectable with appropriate and sensitive tools. We therefore decided to broaden the screening program imposed on transplant candidates in our centre by adding several imaging techniques and tumor marker assays to the proposed scheme at the 24th Bethesda conference (1). The initial findings of our study suggest a common pathway in the etiology of both severe heart failure and cancer. A comparable relation has been put forward between the development of cancer and ischemic heart disease (2).

Between June 1, 1994 and July 31, 2000, 67 patients (pts) referred for heart transplantation underwent an extensive screening program. We used the scheme published in the Task Force by the American College of Cardiology (1) in 1993 as a basis and added several items as shown in Table 1. Mean age was 53.1 years and 43 patients (64%) were male. Etiology of heart failure was ischemic in 39 patients (58%), idiopathic in 22 patients (33%), and of other origin in 6 patients (9%). Of the total group, 36 patients received a cardiac allograft. Nineteen were not accepted for transplantation because they were considered too well (5 pts) or presented with one or more contraindications (14 pts). Five patients died on the waiting list and 6 patients were removed from the list because of significant improvement.

In 10 patients, screening led to the diagnosis of a malignant lesion (cancer group) (Table 2). Nine of these patients presented without any symptoms or clinical evidence of these cancers. Moreover, in each of them, suspicion was raised after one or more of the extra investigations were found to be abnormal. Patients 1, 4, and 7 had a completely normal

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TABLE 1. Extra items added to the screening program

Tumor marker assays
PSA ^a (M)
CEA
Imaging
Abdominal ultrasound
CT scan of the abdomen
CT scan of the thorax
Mammography
Echography of the breast
PAP smear (F)
Colonoscopy in case of + CEA or occult blood in stool
Transrectal prostatic echography if + PSA or prostatic hypertrophy

^a Abbreviations: PSA, prostate specific antigen; CEA, carcino embryogenic antigen; F, females; M, males; PH, prostate hypertrophy.

clinical breast examination. The vaginal in situ carcinoma of patient 2 was not palpable. In patient 3, elevated CEA (17 ng/ml, normal value <6 ng/ml) led to diagnostic colonoscopy. The lung carcinoma detected by CT scan of the thorax in patient 6 was not visible on the routine chest x-ray. Rectal examination in patient 8 revealed an enlarged prostate without suspicious irregularities. The hypernephroma and bladder carcinoma in patients 9 and 10 were first visualised by CT scan of the abdomen. In patient 5, repetitive bouts of low-grade fever eventually led to a diagnostic bone marrow biopsy. The age at the time of diagnosis, etiology of heart failure, sex, and type of malignancy and diagnostic tests are depicted in Table 2. Of this group, eight patients were not accepted for transplantation. Two patients (nos. 2 and 3) were transplanted after a curative resection of an in situ carcinoma was carried out.

At the time of referral, there were no significant differences in sex, heart failure etiology, or known risk factors for malignancy between the non-cancer and the cancer group. Although patients in the cancer group tended to be older, the difference in mean age was only marginally significant (mean age cancer group 59.9±9.4 years, versus non-cancer group 52.3±12.7 years, $P=0.08$, 2-tailed t test). Stratifying patients in younger (i.e., ≤54 years) and older (i.e., ≥55 years) age groups showed a significantly greater proportion of older patients in the cancer group (8/10=80%) compared to the non-cancer group (25/57=44%), $P=0.04$.

Of the transplanted group (mean follow-up of 34 months), four patients underwent resection of a skin tumor (two basal cell carcinomas, two squamous cell carcinomas). A 60-year-

old man developed EBV related non-Hodgkin lymphoma in combination with adenocarcinoma. He is doing well 2 years after a combined therapy (surgical resection and chemotherapy), without disease recurrence. The two patients who received a cardiac allograft despite the finding of a vaginal in situ carcinoma and a neoplastic polyp respectively, are doing well, now more than 4 years after transplantation.

DISCUSSION

Evidence suggests that there is a disproportionately high incidence of neoplasia after allograft transplantation when compared to a matched general population (3). There is indeed ample proof that posttransplant lymphoproliferative diseases (PTLD) and skin cancers are elicited by the use of immunosuppressive drugs. Evidence for a significant increase in the incidence of those neoplasms that are observed frequently in the general population is conflicting. Recently, information gathered from the Cardiac Transplant Research Database (CTRD) (4) revealed the clear distribution of time specific risks for mortality after transplantation. Malignancy (both PTLT and nonlymphoma) was the cause of death in 8.4% of 5,888 heart transplant recipients with a mean follow-up of 39 months. The risk of death from cancer was relatively constant during the first 4 years after transplantation with a slight raise at 5 to 7 years and a marked increase after 7 years (annual risk of death of 7.19 at year 8). Olivari et al. reported an incidence of malignancy of 10% (excluding skin cancer) in their analysis of a group of 228 patients transplanted between 1985 and 1998 (5). Solid organ tumors (SOT) were diagnosed in 16 patients, a median of 48 months after heart transplantation. There was a significant relation with OKT3 treatment. Most of the tumors were squamous cell carcinomas of the lung (five patients). In this series, as well as in others, PTLT occurred earlier than SOT (median follow-up of 10 months versus 48 months for SOT), but prognosis was better (57% after 44 months for PTLT, 37% survival after 25 months for SOT).

Although difficult to prove, it is likely that at least part of the malignancies discovered after transplantation are already present before the administration of immunosuppressant therapy and from then on show an accelerated growth rate. Hence, diagnosis in an early stage is challenging and consequently, a cure remains exceptional (6, 7). It seems therefore appropriate to focus on the detection of previously unknown malignancies during the screening period of potential transplant recipients.

TABLE 2. Clinical and demographic features of patients with malignancy before transplantation

Pt ^a	Sex	Age (yr)	Malignancy	Tx	Etiology of HF	Diagnostic test
1	F	64	Breast ca	Denied	Idiop	Mammo/echo
2	F	59	Vaginal ca	Transplanted	Idiop	PAP
3	M	55	Colon ca	Transplanted	Isch	CEA
4	F	40	Breast ca	Denied	Isch	Mammo/echo
5	M	58	Lymphoma	Denied	Isch	Clinical
6	F	51	Lung adeno ca	Denied	Other	CT-Thorax
7	F	66	Breast ca	Denied	Idiop	Mammo/echo
8	M	72	Prostate ca	Denied	Isch	PSA
9	F	67	Hypernephroma	Denied	Isch	CT-abdomen
10	M	66	Bladder carcinoma	Denied	Idiop	CT-abdomen

^a Abbreviations: Pt, patient; Tx, transplantation; HF, heart failure; F, female; M, male; ca, carcinoma; isch, ischemic; idiop, idiopathic; CEA, carcino embryogenic antigen; PSA, prostate specific antigen.

To exclude patients with clinically silent but relevant malignancies, we decided to broaden the classically adhered screening scheme by adding several imaging techniques and tumor marker assays. The finding that of the 67 patients referred for transplantation, 10 presented to us with a malignant disease, was striking and difficult to explain. In the cancer group, 80% of the patients were 55 years or older, whereas in the non-cancer group this percentage was much lower (44%). However, the incidence of malignancy in both groups is still much higher than the age-adjusted figures for the regional Flemish population (cancer incidence including nonmelanoma skin tumors: 388/100,000 for women, 278/100,000 for men aged 50–54 years, 444/100,000 for women and 500/100,000 for men aged 54–60 years).

With respect to risk factors for the development of solid organ malignancies after heart transplantation, research has mainly focused on smoking habits. Several series have shown that the current or past exposure to tobacco was undoubtedly related to the development of lung cancer after transplantation with an outcome that was invariably infaust (6, 7). There was no difference in heart failure etiology between the cancer and the non-cancer group and thus risk factors such as tobacco use, which could be a common denominator for both ischemic cardiomyopathy and for instance lung cancer, were probably not at play. Particular risk factors for specific malignancies (e.g., familial occurrence of breast or colon cancer) were not present.

Although the long-term benefit and the effect on the occurrence of malignancies of our extensive screening program

should be awaited, it seems without doubt that the patients in the cancer-group would have developed clinically overt disease after transplantation. Therefore, in view of our findings, the elaboration of a more exhaustive schedule of investigations to safely select transplant candidates seems advisable, especially in older patients.

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LATE ONSET OF SEVERE GRAFT-VERSUS-HOST DISEASE IN A PEDIATRIC LIVER TRANSPLANT RECIPIENT

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We report the management of a patient with the late onset of chronic graft-versus-host disease (GVHD) after orthotopic liver transplantation. GVHD is a rare complication of solid organ transplants that usually presents early after transplantation and is fatal in the majority of cases. Our patient differs from the typical patient with GVHD in that the onset of her disease was

very late. Although most treatment to date consisted of an increase in immunosuppressive therapy, our patient showed an excellent response to a reduction. This resulted in the abatement of the symptoms of GVHD and the preservation of her allograft function.

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Cellular graft-versus-host disease (GVHD) is a frequent complication after bone marrow transplantation (1, 2). In addition to the cellular form, another type of GVHD, manifesting as an antibody-mediated hemolytic anemia, is also reported among recipients of liver, intestine, and kidney transplants (3–5). GVHD is acknowledged as a distinctly uncommon entity in solid organ transplant recipients (6–8); however, both humoral and cellular GVHD have been reported in liver transplant patients. Although it is rare in liver transplant recipients, when it occurs, it has uniformly been noted early in the posttransplant period. Additionally, in spite of the institution of aggressive immunosuppressive therapy, GVHD is often lethal (8, 9).