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ORIGINAL ARTICLE

Incidence and prognosis of cancer following heart transplantation using RATG induction therapy

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Summary

Cancer limits survival following heart transplantation. The study's objectives were to evaluate the incidence and risk factors for cancers after heart transplantation and to assess the association between i.v. thymoglobuline induction therapy [rabbit antithymocyte immunoglobulin, (RATG)] and neoplasia. From 1982 to 2002, prospective data were gathered for 207 heart transplant recipients. Except from 1982 to 1987, all patients received a 3-day course of i.v. RATG following transplantation. Forty-three malignant neoplasms (21%) were diagnosed. The most common were: skin (42%), lung (12%), prostate (9%), genitourinary (9%) and lymphoma (5%). Mean length of follow-up after transplantation was 99 ± 57 months. Mean survival after diagnosis was 52 ± 44 months. Multivariate analysis showed no significant increase in the incidence of cancer with recipient age, sex, number of rejection episodes, the type of immunosuppression or the use of RATG. Patients receiving RATG developed their malignancies significantly earlier after transplantation ($P = 0.007$) and succumbed faster after the diagnosis ($P = 0.06$). Cancer is a limiting event for long-term survival after heart transplantation. No individual risk factors allow predicting its development. In the present cohort, RATG does not have carcinogenic effects following transplantation, but is associated with a more precocious development of malignancies.

Introduction

The improvement in graft and patient survivals following heart transplantation is hampered by the high incidence of post-transplant neoplasms [1] varying from 1% to 16% [2,3]. The most common reported tumors are skin cancer and post-transplant lymphoproliferative disorders (PTLD) [4]. A close association between immunosuppression and the development of cancer in graft recipients has been suggested [5], in particular with the use of OKT3 as induction therapy which has been abandoned following reports of an increased incidence of PTLD [6]. Since 1987, heart transplant recipients at the Montreal Heart Institute have been systematically treated with i.v. thymoglobuline induction therapy. The incidence of cancer in patients receiving thymoglobuline induction therapy has been previously reported [7,8]. However, no prior studies have specifically looked at the relationship between thymoglobuline induction therapy and cancer. The objectives of the present study were to evaluate the incidence, the distribution and the risk factors associated with the development of cancers following heart transplantation. Moreover, the possible relationship between thymoglobuline induction therapy and the development of cancer is evaluated.

Materials and methods

Patient population

Between 1982 and 2002, 207 patients received heart transplants with a minimum survival period of 1 month (172

males and 35 females; mean age at transplantation 46 ± 11 years; range: 17–64 years). Prospectively gathered data from the transplantation clinic by a team of specialized nurses were used for the current study. The indications for heart transplantation were ischemic cardiomyopathy (ICM) in 117 patients (56.5%), dilated cardiomyopathy (DCM) in 57 patients (27.5%), and other cardiac diseases in 33 patients (16%). The mean donor age was 29 ± 12 years and the mean ischemic time was 139 ± 49 min. Follow-up of the patients was 100% complete with a mean length of follow-up of 99 ± 57 months. Patients were divided into two groups: patients with a post-transplant neoplasm ($n = 43$, one patient suffered two malignancies) and cancer-free patients ($n = 165$).

Immunosuppression regimen

Between 1988 and 2002, 154 patients were transplanted and received thymoglobuline intravenously (rabbit antithymocyte immunoglobulin – RATG, Pasteur Merieux, Lyon, France) at a dose of 125 mg/day during the first 3 days following heart transplantation. Each infusion of thymoglobuline was pretreated with administration of acetaminophen, diphenhydramine and 125 mg of methylprednisolone. I.v. methylprednisolone (500 mg) was administered during surgery and followed by 125 mg every 24 h for three doses. Oral prednisone (1 mg/kg tapered to 0.1 mg/kg/day), azathioprine (3 mg/kg, $n = 156$ patients) or mycophenolate mofetil (CELLCEPT, Hoffman-La Roche, Mississauga, ON, Canada; 1 g/b.i.d.), which has replaced azathioprine since 1997 (1 g b.i.d., $n = 30$ patients), were started after patient extubation. Oral cyclosporin (Neoral, Novartis Pharma, Dorval, QC, Canada; 2–6 mg/kg) was initiated on postoperative day 2 to day 5 after transplantation [7]. Prior to 1987, and for a brief period in 1994, 45 patients received oral (3–6 mg/kg) or i.v. (1–2 mg/kg in 24 h) cyclosporin from the day of transplantation along with prednisone, but without induction therapy. Oral prednisone was eventually weaned off in selected patients 6–12 months following transplantation.

Whole-blood trough levels of cyclosporin were maintained between 200–300 mmol/l the first 3 months, between 200–250 mmol/l between 3 and 6 months and between 150–200 mmol/l after 6 months following transplantation. Azathioprine was titrated to maintain the white blood cell count >5000 cells/mm^3 and mycophenolate mofetil was administered at a constant dose of 1 g b.i.d.

Patient follow-up

Endomyocardial biopsies were performed weekly for the first month, then biweekly for the next 3 months then at 6 months and 1 year. Acute rejection was diagnosed according to the International Society for Heart and Lung Transplantation (ISHLT) classification [9]. Rejection episodes were treated accordingly: (methylprednisolone 1 g for 3 days or i.v. thymoglobuline for 3 days in refractory rejection). Coronary angiograms were performed 1 year after transplantation and every 2 years thereafter. Pulmonary roentgenograms were obtained every 6 months.

Statistical analysis

Univariate (unpaired *t*-test or one-way ANOVA for continuous variables and Pearson's χ^2 for categorical variables) and multivariate analyses (stepwise logistic regression) were used to assess the relative importance of different variables on the incidence of cancer in our transplant population. The variables analyzed included: age at transplantation, sex, ischemic time, the underlying disease, RATG administration, various immunosuppressants and the frequency of rejection episodes. The results are expressed as mean ± SD or as percentages for categorical variables. A *P*-value of <0.05 was considered statistically significant.

Results

Cancer data

Forty-three malignant neoplasms were diagnosed in 42 of 207 patients (21%). The incidence of solid tumors (excluding skin and PTLD) was 11% (23/207). No differences were noted between both groups (cancer versus cancer-free patients) with regard to recipient age (46.3 vs. 46.5 years; $P = 0.9$), sex ($P = 0.9$), the underlying pathology ($P = 0.5$), smoking history ($P = 0.2$) and the number of treated rejection episodes in the first year ($P = 0.96$) (Table 1). No predictive factors were isolated on multivariate analysis.

With regard to patients developing a neoplasia ($n = 43$), the distribution of different cancers was as follows: skin (basal/squamous: 16/1) (42%), lung (12%), prostate (9%), genito–urinary (9%), PTLD (5%), central nervous

Table 1. Characteristics of patients with and without cancer.

Patient characteristics	Cancer ($n = 43$)	No cancer ($n = 165$)	*P*-value
Recipient age (years)	46.5 ± 12.5	46.6 ± 10.0	0.90
Recipient gender (% male)	82.5%	83.2%	0.91
Smoking at time of transplantation (%)	35 (81)	112 (67)	0.3
Nb of treated rejection episodes in the first year	0.98 ± 1.03	0.96 ± 1.12	0.96
RATG use (%)	70.0%	80.2%	0.16

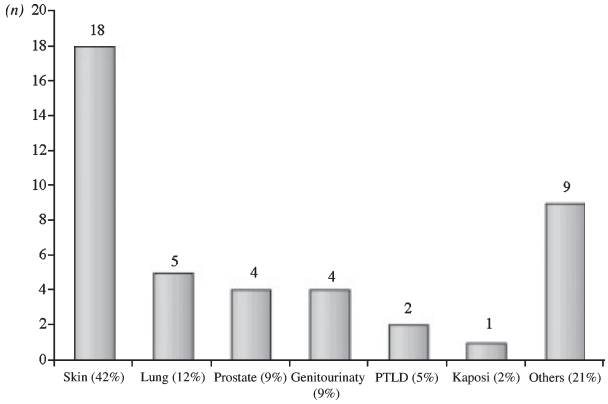

Figure 1 Distribution of various types of malignancies among cancer patients ($n = 43$). PTLD, post-transplant lymphoproliferative disorder.

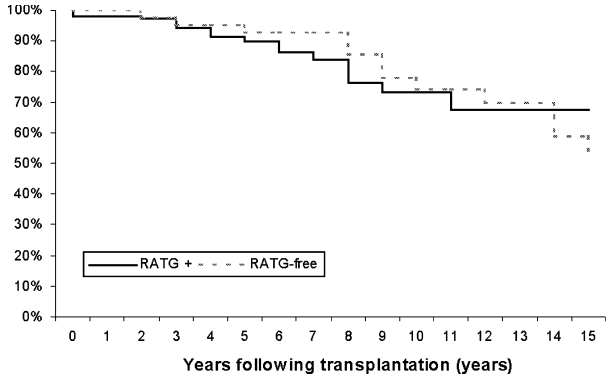

Figure 2 Actuarial survival free from cancer in patients receiving RATG versus patients not receiving RATG ($P > 0.05$).

system (5%), head and neck (5%), bowel (5%), Kaposi's sarcoma (2%) and others (pancreas, renal, hematopoietic) (6%) (Fig. 1). The mean interval from transplantation to diagnosis was 86 ± 45 months (range, 6–180 months). No differences were found among different cancers regarding the time to diagnosis after transplantation ($P = 0.27$). No significant demographic differences were found between different cancer groups in terms of sex, donor age, recipient age, ischemic time or number of treated rejection episodes. Mortality rate following a diagnosis of cancer over the follow-up period was 27%. Mean survival time in these patients was 34 ± 11 months. Mean survival after a diagnosis of lung cancer was 20 ± 19 months, significantly shorter than all other malignancies combined ($P = 0.009$). Skin cancer carried the best prognosis with an 88% actuarial survival at 10 years.

Effects of immunosuppression

When examined separately, no significant association was found between the administration of any particular drug and the development of a neoplastic lesion. More specifically, no association was observed between the use of azathioprine and the occurrence of skin cancer ($P = 0.8$), and no relationship between the development of PTLD and the use of cyclosporin was noted despite the long follow-up period. Because of the small number of cases of PTLD observed in this cohort, ($n = 2$) no analysis was undertaken to evaluate the potential role of different immunosuppressive regimens.

Role of thymoglobuline induction therapy

There was no association between the use of thymoglobuline induction therapy and the occurrence of cancer (17% in patients receiving RATG versus 27% in patients not receiving RATG; $P = 0.16$) (Fig. 2). This difference is not statistically significant, but considering the number of patients, the power of the analysis is 30% ($\beta = 0.70$). Furthermore, no correlation was observed with any specific type of cancer. Among the two cases of PTLD, one developed in the pre-RATG cohort and the other in a patient who received RATG. Two observations are noteworthy regarding RATG induction therapy (Table 2). Firstly, patients receiving RATG developed their malignancies significantly earlier after transplantation than the

Table 2. Characteristics of patients receiving or not receiving RATG.

	RATG+ ($n = 162$)	No RATG ($n = 45$)	*P*-value
Cancer (%)	17.3%	26.7%	0.16
Recipient age (years)	47.7 ± 10.4	42.0 ± 9.9	0.001
Donor age (years)	30.6 ± 12.3	25.0 ± 8.2	0.0004
Gender (% male)	83.9%	82.2%	0.86
Smoking at time of transplantation (%)	120 (74)	27 (60)	0.5
Mean ischemic time (min)	140.1 ± 49.7	135.1 ± 48.1	0.55
Time to cancer diagnosis (months)	73.4 ± 37.0	114.7 ± 50.9	0.007
Time from cancer diagnosis to death (months)	19 ± 27	61 ± 36	0.06
No of treated rejection episodes (first year)	0.9 ± 1.1	1.2 ± 1.2	0.08

Table 3. Distribution of different types of cancer according to RATG administration.

Type of cancer	RATG+ ($n = 31$)	No RATG ($n = 12$)	*P*-value
Skin	12 (40)	5 (42)	0.90
Lung	4 (13)	1 (8)	0.6
PTLD	1 (3)	1 (8)	0.3
Other	14 (44)	5 (42)	0.9

others (73 vs. 115 months; $P = 0.007$). Secondly, those same patients succumbed faster after the diagnosis was established (19 vs. 61 months; $P = 0.06$). The distribution of cancers between patients receiving RATG and those not receiving RATG is shown in Table 3 ($P = \text{NS}$). Despite the fact that patients receiving RATG were significantly older than their counterparts (47.7 ± 10.4 vs. 42.0 ± 9.9 years; $P = 0.001$), the distribution of the various cancers was comparable between both categories of patients.

Discussion

Occurrence of cancer after heart transplantation is a well-described consequence of immunosuppression [1] with a reported incidence of 1–16% [2,3]. In fact, Opelz and Dohler [10] have demonstrated through the collaborative transplant study (CTS) registry that the incidence of cancer following heart transplantation is two- to threefold higher than in kidney transplantation, regardless of age. The 21% incidence of malignancy after heart transplantation in this series is higher than in most studies, including Mihalov *et al.* [11] who reported a rate of 15.6% in 307 cardiac transplant recipients. This higher incidence may be due to several reasons: a longer and closer follow-up and a more complete reporting of the malignancies. None of the patients or their donors had previously documented malignancies, which are associated with a recurrence rate of up to 45% in cardiothoracic transplant recipients [12]. The difference in incidences is mainly incumbent on the 11% incidence of solid tumors, strikingly higher than Goldstein *et al.*'s [13] 3% (21/633) or Pham *et al.*'s [14] reported 6% incidences (36/608), despite a comparable follow-up period of 17 years and older age of their cancer population at transplantation (51 vs. 45 years). Although earlier reports have linked the use of cyclosporine to the development of malignancies, namely PTLDs [15], no correlation to any specific malignancy was found. This duplicates the findings of Olivari *et al.* [2] who found no relationship between cyclosporin use and the occurrence of lymphomas. However, a recent study on renal transplant recipients suggests an increased incidence of cancer in transplant recipients receiving cyclosporin if older than 45 years [16]. The present study does not support this correlation (25% in <45 years of age vs. 26% in ≥45 years; $P = 0.9$). Furthermore, the use of azathioprine was not associated with an increased occurrence of skin cancer despite its possible link to the latter due to the photosensitizing effects of its metabolites [17].

The systematic use of i.v. thymoglobuline induction therapy in our cohort since 1987 ($n = 162$) allows a thorough study of its effects in heart transplant recipients. Reports have long diverged over the association between induction therapy and cancer, especially since Swinnen *et al.* [6] showed in 1990 an increased incidence of PTLD with the use of OKT3, which halted its use as induction therapy following transplantation. However, in the present series, no association was found between the use of i.v. thymoglobuline induction therapy and the development of cancer ($P = 0.16$). Despite the lack of significant association in terms of incidence, patients receiving RATG had a more precocious development and more dismal prognosis of the malignancy. These findings could potentially be explained by the fact that patients receiving RATG were significantly older than their counterparts (48 vs. 42 years; $P = 0.001$) putting them at a higher risk of developing cancer, as in the general population. The unfavorable course might be consecutive to developing more aggressive neoplasms such as lung cancer which are associated with significantly shorter survival, and occur more frequently in older patients. In fact, four of five lung cancer victims were in the RATG group and averaged 49 years of age. However, no correlation with recipient age was observed when comparing cancer and cancer-free patients. Moreover, because of the small number of patients diagnosed with cancer, it was difficult to establish a statistically significant correlation between RATG use and the development of a certain type of cancer.

Of all cancers, lung carcinomas were the most lethal with a significantly shorter survival rate after diagnosis (20 ± 19 months vs. 52 ± 44 months; $P = 0.009$). These data concur with previous published studies on the incidence of solid tumors after transplantation which reported the dismal survival of lung cancers in immunosuppressed patients [13,14]. In the present cohort, a positive smoking history was considered when patients were smokers at the time they were listed for transplantation. Despite a trend for patients developing cancer to have a higher incidence of smoking history, smoking was not found to be a predictive factor for cancer in this patient population ($P = 0.2$). Other groups, however, have previously addressed this issue and have established a relationship between smoking and cancer due to the combined negative effects of tobacco use on the immune system and of pharmacologically induced immunosuppression.

Post-transplant lymphoproliferative disorders have long been a major impediment to long-term survival with a reported incidence of up to 14% of all post-transplantation cancers. This high incidence was attributed in some reports to the use of i.v. induction therapy following transplantation and to higher doses of cyclosporin formerly used. In fact, these practices explain the higher prevalence of PTLDs in cardiac transplant recipients compared with renal transplant recipients (6.5% vs. 0.7%) [11]. In this series, PTLD represented only 1% of all transplant recipients suggesting that the use of i.v. induction therapy using RATG did not promote post-transplantation cancers.

Limitations

Although the data were gathered prospectively, the retrospective nature of this analysis carries the limitations of any such study design. The modern era of cardiac transplantation is relatively young dating back to the early 1980s. Many changes, although not dramatic, have taken place since that time. Although the patient population studied in the present report is not perfectly homogeneous, it is a good reflection of cardiac transplantation recipients worldwide. Although we attempted to eliminate any confounding factors through statistical analysis when comparing patients receiving RATG induction therapy and those not receiving it, the results should be carefully interpreted as they are noncontemporary populations. Also, the limited number of patients not receiving RATG results in reduced statistical power ($\beta = 0.70$) therefore mandating a careful analysis of the results. Lastly, despite the incidence of cancer being significant in this cohort, the absolute numbers remain limited therefore making it difficult to compare various subgroups of immunosuppressive regimens as to their association with cancer development.

Conclusion

In conclusion, the long-term prognosis following heart transplantation is strongly affected by the occurrence of malignancy in immunosuppressed transplant recipients. Despite the long follow-up period, no individual predictive factors were identified. Long-term cumulative immunosuppressive load over the years remains the most likely culprit. Nonetheless, constant vigilance is warranted throughout the patients' follow-up after transplantation to guarantee early detection and treatment initiation. In light of the study's statistical limitations, the use of i.v. thymoglobuline for induction therapy in the present cohort has no carcinogenic effect *per se*, but is associated with a more precocious development of malignancies carrying a worse prognosis. The advent of more specific immunosuppressants in the future may allow better preservation of the immune mechanisms involved in cancer surveillance and potentially decrease the incidence of post-transplantation malignant disease.

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References

1. Cole WH. The increase in immunossuppression and its role in the development of malignant lesions. *J Surg Oncol* 1985; **30**: 139.
2. Olivari MT, Diekmann RA, Kubo SH, Braunlin E, Jamieson SW, Ring WS. Low incidence of neoplasia in heart and heart-lung transplant recipients receiving triple-drug immunosuppression. *J Heart Transplant* 1990; **9**: 618.
3. Couetil JP, McGoldrick JP, Wallwork J, English TA. Malignant tumors after heart transplantation. *J Heart Transplant* 1990; **9**: 622.
4. MacLeod AM, Catto GR. Cancer after transplantation. *Br Med J* 1988; **297**: 4.
5. Penn I. Cancers complicating organ transplantation. *N Engl J Med* 1990; **323**: 1767.
6. Swinnen LJ, Costanzo-Nordin MR, Fisher SG, *et al.* Increased incidence of lymphoproliferative disorder after immunossupression with the monoclonal antibody OKT3 in cardiac-transplant recipients. *N Engl J Med* 1990; **323**: 1723.
7. Carrier M, White M, Perrault LP, *et al.* A 10-year experience with intravenous thymoglobuline in induction of immunosuppression following heart transplantation. *J Heart Lung Transplant* 1999; **18**: 1218.
8. Zuckermann AO, Grimm M, Czerny M, *et al.* Improved long-term results with thymoglobuline induction therapy after cardiac transplantation: a comparison of two different rabbit-antithymocyte globulines. *Transplantation* 2000; **69**: 1890.
9. Billingham ME, Cary NR, Hammond ME, *et al.* A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: Heart Rejection Study Group. *J Heart Tranplant* 1990; **9**: 587.
10. Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. *Am J Transplant.* 2004; **4**: 222.
11. Mihalov ML, Gattuso P, Abraham K, Holmes EW, Reddy V. Incidence of post-transplant malignancy among 674 solid-organ-transplant recipients at a single center. *Clin Transplant* 1996; **10**: 248.

12. Buell JF, Trofe J, Hanaway MJ, *et al.* Transmission of donor cancer into cardiothoracic transplant recipients. *Surgery* 2001; **130**: 660.
13. Goldstein DJ, Williams DL, Oz MC, Weinberg AD, Rose EA, Michler RE. De novo solid malignancies after cardiac transplantation. *Ann Thorac Surg* 1995; **60**: 1783.
14. Pham SM, Kormos RL, Landreneau RJ, *et al.* Solid tumors after heart transplantation: lethality of lung cancer. *Ann Thorac Surg* 1995; **60**: 1623.
15. Wilkinson AH, Smith JL, Hunsicker LG, *et al.* Increased frequency of posttransplant lymphomas in patients treated with cyclosporine, azathioprine, and prednisone. *Transplantation* 1989; **47**: 293.
16. Tremblay F, Fernandes M, Habbab F, deB Edwardes MD, Loertscher R, Meterissian S. Malignancy after renal transplantation: incidence and role of type of immunosuppression. *Ann Surg Oncol* 2002; **9**: 785.
17. Hemmens VJ, Moore DE. Photochemical sensitization by azathioprine and its metabolites-II. Azathioprine and nitroimidazole metabolites. *Photochem Photobiol* 1986; **43**: 257.