Solid Tumor Malignancies after Cardiac Transplantation

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A. Study Purpose and Rationale

The purpose of this study is to investigate the incidence of solid tumor development after cardiac transplantation in a single institution, and then to compare this incidence to that of the general population in matched controls.

According to the Registry of the International Society of Heart and Lung Transplantation conditional median survival for cardiac transplant recipients who live to the end of the first year is 11.6 years, an achievement which reflects, amongst other factors, the improvement of immunosuppressive therapy. Malignancy is, along with cardiac allograft vasculopathy, a leading cause of death in long term survivors of heart transplant, responsible for nearly 33% of such events. While transplant coronary artery disease was a novel finding that acquired extensive clinical efforts and research, malignancy has remained a daunting dilemma that at times requires modification of the immunosuppressive regimen, and has now surpassed TCAD as the leading cause of death of recipients >3 years post transplant. The International Transplant Tumor Registry founded by Dr. Isreal Penn in 1967 has demonstrated that malignancies are common following organ transplantation with 4-18% of candidates developing de novo malignancies. Overall this makes for a threefold to fourfold increased incidence of cancer compared with age-matched controls in the general population. A great majority of his findings were based on renal allograft recipients. Historically, lymphoproliferative disorders and skin cancers predominate and are long recognized complications of immunosuppressive therapy. The incidence of SCC is 40-250x greater than the general population, while the incidence of BCC is 10x greater. Lymphomas, accounting for only 5% of all cancers of the general population, constitute 22% of the cancers that occur in transplant populations, and up to 39% in cardiac transplants. Post-transplant lymphoproliferative disorders consist mainly of abnormal proliferations of B lymphocytes, with a central pathogenic role believed to be played by EBV. The many factors that are believed to add to this incidence are impaired T cell surveillance, immunosuppressive drugs, CMV infection, B-cell proliferating interleukins, long term antigenic stimulation by the allograft, and the activation of cellular oncogenes. The use of cytolytic induction therapy, specifically with OKT3, has also been established to increase risk of PTLD.

The incidence of non-cutaneous solid tumors, such as those commonly seen in the general population, was described by Dr. Penn to be similar in the transplant population in 1993. Since this time, non-cutaneous solid tumors after cardiac transplantation have received little attention. There is also no consensus as to an association between immunogenic therapy and solid tumors. However there have been multiple institutional reviews and case reports that have shown increased incidences of solid tumors after cardiac transplant. Two reports from major US transplant centers in 1995 detailed a prominence of lung cancers in their populations, postulating

the relationship to smoking history, however not reporting such data. As well, they noted an advanced disease stage and poor prognosis in these patients. However there has not been a comparison made with the general population in a group matched for such factors as age, sex, race, residence, and smoking history. A recent large cohort study of cancer incidence in renal transplant patients, was able to depict an increased incidence in multiple solid tumors post transplant using a standardized general population control. The data suggested a greater role than previously appreciated of the interaction between the immune system and common viral infections in the etiology of cancer.

There are multiple implications for management and future research were there to be an increased solid tumor incidence (as well as lymphoproliferative and skin) found in cardiac transplant recipients as well. More effort would be focused on avoiding use of cytolytic therapies, on reducing immunosuppressive regimens, and on more accurate testing of rejection, in order to tailor immunosuppression. Studies could focus on specific immunosuppressants and cancer risk, duration of therapy and risk, and more intensive cancer screening.

B. Study Design and Statistical Analysis

This is a retrospective chart review cohort study of cardiac allograft recipients at Columbia-NY Presbyterian Hospital between 1994-2006 who have developed noncutaneous solid tumors post transplant. The 856 adult patients that have been transplanted over this period will be considered the population at risk. Patients under the age of 18 and those with a prior history of cancer will be excluded from the study. The patients that have gone on to develop solid tumors will be identified based on individual cardiology attending's running logs of such data, as well as WEBCIS review based on ICD-9 code for cardiac transplant + cancer, and clinical chart review. Noncutaneous solid tumors will be defined as all tumors except for lymphomas, leukemias, and skin cancers other than melanoma. The incidence of development of these tumors within the cardiac transplant population will then be compared to the incidence of the general US population based on statistics from the SEER (Surveillance Epidemiology and End Results) database of the NCI. The following data points will be collected for each subject to be assessed as covariates: age, sex, race, BMI, state of residence, etiology of heart failure, smoking history, alcohol history, family history of cancer, pregnancies, baseline immunosuppressive therapy, use of induction therapy, number of rejection episodes, viral infection status (EBV, CMV, Herpes, Hepatitis B, Hepatitis C), and tumor markers prior to transplant (PSA).

The mean age of the transplant population of Columbia-NYP Hospital from 1994-2006 is 52, with a median of 55, and mode of 59. Based on this, we used the incidence of cancer of the US general population based on the SEER cancer statistics review "age specific incidence" of the population from age 50-59 of "all sites" from 2000-2003 and subtracted incidence of leukemias + lymphomas to get an incidence of 0.0135. As our transplanted population represents an above

average proportion of smokers, at 51% prevalence, we consulted the literature to adjust for a likely increased incidence based on the presence of such a strong independent risk factor. A study looking at cancer incidence in a cohort of 29,000 Finnish male smokers aged 50-69 found an incidence of 0.20. While another study of 8,000 Japanese American men above age 30 in Hawaii found an incidence of 0.22 in smokers. If we were to take this estimate into account we could assume 51% of the transplant population had a 20% incidence while the other 49% had the 1.3% incidence of the general population, to come to a conservative estimate of 0.107.

Given the transplant population gives us an absolute number of subjects, with 856, we can conduct a Chi-square analysis for effect size as follows (with alpha set at 0.05 and power set at 80%): Number of subjects= 856, Comparison proportion =0.107; therefore the smallest detectable proportion for our study group is $p<0.079$ and the largest is $p>0.14$. Thus in order to detect a significant increased incidence of solid tumors among our transplant population an incidence rate greater than 14% must be found.

Under the presumption that the general population statistic takes into account smoking to a degree that reflects our population's prevalence, under the same Chi-square analysis using only the comparison proportion of 0.0135, our detectable proportions become 0.004 and 0.028, making a significant incidence rate 2.8%.

Subsequent analysis after data collection will be done based on standardized incidence ratios, the ratio of observed to expected numbers of cancers. Population cancer incidence rates will be obtained through use of the SEER database by 5 year age groups, sex, year, and state for all cancer sites. The expected numbers of incident cases will be calculated by multiplying person-years at risk (years at risk=years since date of transplant), by the corresponding population cancer incidence rates. Also, odds ratios will be computed using case-control analysis with transplanted patients who did not develop solid tumors post transplant.

C. Study Procedure

This study will be a retrospective cohort study that begins with the identification of those cardiac transplant recipients that have developed solid tumors via attending records, WEBCIS search via ICD-9 codes, and clinical chart review. A list of patient medical record numbers that meet inclusion criteria will be generated and their medical records reviewed, both paper and electronic for collection of data points described above, collected previously during pre-transplant evaluations. The entire transplanted population will also undergo retrospective record review in order to establish a database including age, sex, residence, smoking history.

D. Study Drugs

N/A

E. Medical Devices

N/A

F. Study Questionnaires

N/A

G. Study Subjects

The study population consists of those patients that have received a cardiac transplant at Columbia-NYP Hospital between 1994-2006, and have survived >1 month after transplant. The study will include all transplanted patients, regardless of sex, race, ethnicity, socioeconomic background, or religion. Patients under the age of 18, as well as those transplanted patients with a prior history of malignancy, except for nonmelanoma skin cancers, will be excluded from the study.

H. Recruitment of Subjects

This is a retrospective chart review. No patients will be recruited for participation in the study.

I. Confidentiality of Study Data

Each patient will be assigned a unique study number in order that no identifying data will be used for coding. All data will be coded. All data will be stored on a secure password protected computer and all data on disc will be encrypted.

J. Potential Conflict of Interest

None

K. Location of the Study

The data collection will take place in Columbia University Medical Center.

L. Potential Risks

N/A

M. Potential Benefits

There is no individual benefit to patients that are to be included in this retrospective review. There is a larger scale benefit in identifying a potential increased incidence in solid tumor incidence in cardiac transplant patients. Such results will help address whether future patients should be more aggressively screened, and whether established immunosuppressant regimens should be re-evaluated.

N. Alternative Therapies

N/A

O. Compensation to Subjects

N/A

P. Costs to Subjects

N/A

Q. Minors as Research Subjects

N/A

R. Radiation or Radioactive Substances

N/A

References

Penn I. Cancer complicating organ transplantation. N ENG J Med; 323: 1767-9.

Penn I. Solid Tumors in cardiac allograft recipients. Ann Thorac Surg 1995:60: 1559-1560.

Rinaldi M, Pellegrini C, D'Armini AM, et al. Neoplastic disease after heart transplantation:single center experience. Eur J Cardiothoracic Surg 2001;19:696-701

Goldstein DJ, Williams DL, Oz MC, Weinberg AD, Rose EA, Michler RE. De novo solid malignancies after cardiac transplantation. Ann Thorac Surg 1995; 60:1783-9

Pham SM, Kormos RL, Landreneau RJ Kawai A, Gonzalez-Cancel I, Hardesty RL, Hattler BG, Griffith BP. Solid tumors after heart transplantation: lethality of lung cancer. Ann Thorac Surg 1995; 60:1623-1626.

Taniguchi S, Cooper DKC, Chaffin JS, Zuhdi N. Primary bronchogenic carcinoma in recipients of heart transplants. Transpl Int 1997; 10:213-316.

Ippoliti G, Rinaldi M, Pellegrini C, Vigano M. Incidence of cancer after immunosuppressive treatment for heart transplantation. Critical Reviews in Onc/Hem 2005; 56:101-113.

Chyou PH, et al. A prospective study of the attributable risk of cancer due to cigarette smoking. Am J Public Health. 1992 Jan; 82(1):37-40.

Malila N, et al. Cancer incidence ina cohort of Finnish male smokers. Eur J Cancer Prev. 2006 Apr;15(2):103-7.

Vajdic CM, et al. Cancer incidence before and after kidney transplantation. JAMA. 2006. Dec; 296; 23: 2823-31.

Hauptman PJ. It is time to stop ignoring malignancy in heart transplantation: A call to arms. Journ of Heart and Lung Trans. 2005. Aug; 1111-2.