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Heart Transplant Survival Outcomes for Adriamycin Dilated Cardiomyopathy

Andrew J. Lenneman, MD^{a,d,f}, Li Wang, MS^{c,d}, Mark Wigger, MD^{a,d}, Haydar Frangoul, MD^{b,d}, Frank E. Harrell, PhD^{c,d}, Cheri Silverstein, MD^e, Douglas B. Sawyer, MD, PhD^{a,d}, and Carrie G. Lenneman, MD, MSCI^{a,d,f}

^aDivision of Cardiovascular Medicine, Nashville TN

^bDivision of Pediatric Hematology Oncology, Nashville TN

^cDepartment of Biostatistics, Nashville TN

^dVanderbilt University School of Medicine, Nashville TN

^eDivision of Cardiovascular Medicine, University of California Los Angeles, Los Angeles CA

^fDivision of Cardiovascular Medicine, University of Louisville School of Medicine, Louisville KY, USA

Abstract

In 2015 there will be an estimated 11.3 million cancer survivors. With a growing population of cancer survivors, it is imperative to understand treatment options and outcomes for chemotherapy related cardiomyopathy. Anthracycline (AC) based chemotherapy causes heart failure (HF) in approximately 5% of patients. Orthotopic heart transplant (OHT) is an option for cancer survivors in complete remission who develop end-stage HF. We examined retrospective OHT data collected from United Network of Organ Sharing (UNOS) from 1987–2011. The primary aim was to characterize the survival in patients with either the primary diagnosis of “Dilated Cardiomyopathy: Adriamycin” (DCA) versus “all other” causes of cardiomyopathy. The secondary aim was to define the differences in primary cause of death and to describe the temporal relationship of DCA OHT. The UNOS database identified 453 OHT for the diagnosis of DCA and 51,312 OHT for all other causes of cardiomyopathy. DCA group was significantly younger with a higher percentage of females. After adjusting for age, gender, and previous history of malignancy, the 10-year survival curves show that DCA patients have an improved survival over all other causes cardiomyopathy (HR 1.28, $p = 0.026$). There was no difference in the primary cause of death between the 2 groups. There was a statistically significant increasing temporal trend in the number of OHT for the diagnosis DCA. In conclusion patients who undergo OHT for DCA have a favorable 10-year survival, making OHT a good therapeutic option for end-stage HF due to anthracyclines. Additionally there was no increased risk of cancer related deaths in the DCA, demonstrating that recurrent malignancy does not impact long-term survival. Temporal trends demonstrate that DCA remains a significant problem for cancer survivors.

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Dr. Carrie Anna Geisberg Lenneman, Vanderbilt University School of Medicine, Division of Cardiovascular Medicine, 2220 Pierce Avenue, 361 PRB, Nashville, TN 37232-6300 carrie.lenneman@louisville.edu Phone: (502)-909-4858 Fax: (615)-936-2029.

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Keywords

cancer survivor; anthracycline; cardio-oncology; heart failure

Introduction

As the number of cancer survivors continues to grow, it is critically important to understand treatment options and outcomes for chemotherapy related cardiomyopathy. Anthracyclines (AC) remain a common chemotherapy agent for breast cancer, sarcomas, lymphomas and leukemias with an average incidence of heart failure (HF) in 5.1% of individuals treated with cumulative dose of 400 mg/m² (1, 2). Adriamycin, the first and most widely used AC was approved in 1974 and is known to cause progressive cardiomyopathy in a cumulative dose-dependent manner. Orthotopic heart transplant (OHT) is an option for cancer survivors considered in complete remission who are otherwise eligible for transplantation. We sought to describe the long-term OHT survival outcomes of patients with AC-induced cardiomyopathy, examine the differences in primary cause of death and characterize the temporal trends.

Methods

UNOS provided de-identified patient data (Standard Transplant Analysis and Research [STAR] files with follow-up data) from the thoracic organ transplant registry from the years 1987 to 2011, with follow-up through October 2011. The data include all U.S. patients undergoing thoracic organ transplantation and who were reported to the Organ Procurement Network during the time period. No center or patient identifiers were included.

We conducted a retrospective review of the UNOS registry and follow-up from October 1st 1987 through October 31st 2011. The time-points were chosen to determine long-term survival outcomes in OHT patients and to demonstrate the trends in number of OHT performed due to AC exposure. From the thoracic registry we selected only patients who underwent an OHT for analysis. The UNOS OHT candidate registration forms contains 35 diagnostic classifications for the various causes of cardiomyopathy. From the diagnosis at the time transplant registration we stratified the cohort into two groups by diagnosis: Dilated Cardiomyopathy: Adriamycin (DCA) versus all other causes of cardiomyopathy. All first-time OHT patients > 1 year of age were included. A broad age range was included to account for the high prevalence of pediatric cancer survivors.

Baseline demographic and clinical factors were examined. The database contained age, gender, race, and various medical conditions at the time of transplant for DCA and all other cardiomyopathy. While incomplete with some missing data, the UNOS database contains information regarding cancer history at the time of transplant. The primary end-point was primary cause of death during the study period. We categorized the causes of death into: graft failure (acute and chronic), cardiovascular, pulmonary, infection (bacterial, viral, and fungal), renal failure, liver failure, multi-organ failure, CNS, suicide and malignancy. We used the database to determine if there was difference in OHT survival in patients with DCA versus all other causes of cardiomyopathy.

The primary goal of the study was to determine if there is any difference in 10-year survival between DCA and all other cardiomyopathy. The initial hypothesis was that DCA patients would have decreased long-term survival. All patients with follow-up times longer than 10-years were censored at 10-years. We calculated both the unadjusted and the adjusted hazard ratio for myopathy group using Cox proportional hazard model. The other covariates adjusted included age, gender, and previous history of malignancy. Additionally we

performed a linear model to evaluate the percentage of DCA heart transplant performed from 1987 to 2011.

Descriptive statistics were presented as median (interquartile range [IQR]) or percentage (N) as appropriate. Wilson's score method was used to calculate 95% confidence interval for percentages. Comparisons of baseline characteristics between study groups were performed using Wilcoxon rank sum test for continuous variables and the Pearson's Chi-squared test for categorical variables. Cox proportional hazards regression model was used to assess the difference in 10-year survival between the two groups with adjustment of age, gender, and previous malignancy. Age was modeled as continuous variable with appropriate transformation using restricted cubic splines with five knots to account for nonlinear relationship. Proportional hazards assumption was assessed by residual plot as well as statistical test. All tests were two-tailed, with a significance level of 5%. Statistical analysis was performed with statistical software SPSS Statistics version 17.0 (SPSS Inc, Chicago Illinois) and the statistical programming language R, version 2.15.1 (R Development Core Team, Vienna, Austria)(3).

Results

From October 1987 to October 2011 51,765 patients underwent primary OHT. A total of 453 were transplanted for DCA. The median age of DCA OHT recipients was significantly younger than all other cardiomyopathy (median [IQR]: 44 [23,56] vs. 52 [38,59], respectively; $p < 0.001$) with a higher percentage of females (Table 1). There was no difference in racial or ethnic diversity between the two groups (Table 1).

As expected DCA cohort had a higher percentage of patients with previous history of breast cancer and leukemia. There was no statistically significant difference in comorbidities of diabetes or cerebrovascular disease between the two groups. At the time of heart transplant the DCA group appeared less critically ill with lower number of individuals in the intensive care unit, however a higher number of DCA patients were on IV inotropes at the time of heart transplant (Table 1).

Since 1987, an increasing percentage of OHT have been performed due to DCA ($p < 0.001$) (Figure 1). Whereas, the temporal distribution of OHT for idiopathic cardiomyopathy which has remained relatively constant with average of 700 OHT per year.

There was no statistically significant difference in primary cause of death between the DCA and all other cardiomyopathy ($p = 0.486$). Cardiovascular cause of death was highest in both groups (23% DCA [95% CI 0.17 – 0.30] and 21% all other CM [95% CI: 0.20 – 0.21]). Death due to malignancy was the same between the two groups.

The unadjusted 10-year OHT survival showed no statistically significant difference between all other cardiomyopathy versus DCA (HR 1.14, [95% CI: 0.94 – 1.39], $p = 0.198$). After adjusting for age, gender, and previous history of malignancy, there was evidence that DCA patients who underwent OHT had an improved 10-year survival over all other causes of CM (HR 1.28, [95% CI: 1.03–1.59], $p = 0.026$) (Figure 2).

Discussion

Over the past several decades the number of cancer survivors are steadily increasing due to improved detection and treatments. Anthracyclines (AC) remain an important agent for the treatment of lymphomas, leukemia, sarcomas and breast cancer. Patients with anthracycline-induced cardiomyopathy have significantly worse outcomes compared with other causes of

cardiomyopathy (4). With a growing number of cancer survivors, anthracycline cardiomyopathy has become an increasingly common cause of OHT (Figure 1).

OHT recipients have a higher risk of developing cancer following heart transplant due to chronic immunosuppression (5). Therefore, heart transplant candidates with prior malignancy are thoroughly screened to assess risk of recurrence. This study demonstrates that patients with DCA, despite prior history of cancer have similar long-term survival in comparison to patients with other forms of cardiomyopathy. This study does not report data on risk of cancer development due to immunosuppression, only those who died from cancer. The survival data is promising for cancer survivors illustrating the prognosis of advanced HF due to anthracycline cardiotoxicity can be modified by undergoing OHT. Additionally the UNOS data demonstrates no increase in death from malignancy as the primary cause of death between DCA and all other cardiomyopathy.

The optimal cancer-free interval prior to heart transplantation has not been determined. Current data support the strategy of thorough screening to ensure cancer remission in heart failure patients prior to heart transplant. With encouraging survival rates in DCA and a growing population of cancer survivors, it is likely that transplant centers will evaluate increasing numbers of patients who have survived treatment for a previous malignancy.

The annual number of heart transplants performed in the U.S. has remained constant for the last 15 years. An increasing percentage of OHT are performed due to refractory HF secondary to AC-induced cardiomyopathy. This reflects the growing population of cancer survivors as well as improved recognition and proper classification of DCA. Despite decades of use, anthracycline cardiotoxicity remains a significant clinical problem that we have not learned how to effectively prevent.

Since the original analysis and presentation of our data, Oliveira and colleagues recently published a complimentary study demonstrating similar short-term survival outcomes for chemotherapy-induced cardiomyopathy patients undergoing heart transplant (6). Our analysis shows that even long-term follow-up (10-years from OHT) is favorable in DCA. Additionally this study is unique in its emphasis on the growing temporal trend in the number of OHT performed for DCA patients.

We recognize several limitations of our study. First, the study is retrospective and cannot account for undocumented differences in patient characteristics. Large administrative clinical registries like UNOS are reliant on accurate coding of information. Errors and variance in the data undoubtedly exist and we have assumed that these are randomly distributed and do not lead to significant bias in our conclusions. By using a nationwide registry, we are dependent on the variables, definitions, and measurement outcomes present in the dataset. We acknowledge that over the 24 years of UNOS data collection there have been significant advancements in the diagnosis, management, and surgical techniques of OHT. However in order to examine the 10-year long-term survival in OHT, the time frame was not limited to the most recent decade. Despite these limitations, the study has several advantages. UNOS dataset provides an unbiased multi-institution examination of survival outcomes in heart transplant recipients. Short of a randomized controlled trial, we believe that a large nationwide retrospective study with compensatory statistical methodology constitutes a reasonable approach for examining differences between DCA and all other causes of CM.

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Figure 1.

Depicts a statistically significant increase in the percentage of orthotopic heart transplant per year from 1987 – 2011 for the diagnosis dilated cardiomyopathy: adriamycin (DCA) ($p < 0.001$).

Figure 2.

Demonstrates overall long-term (10 year) survival. A) Kaplan-Meier estimate for overall survival between dilated cardiomyopathy: adriamycin (DCA) and all other causes of cardiomyopathy (CM) (HR 1.14, [95% CI: 0.94–1.39], $p=0.198$). B) Overall survival model adjusted for age, gender, and history of malignancy, demonstrates improved long-term survival for DCA over all other causes of cardiomyopathy (HR 1.28, [95% CI: 1.03–1.59], $p=0.026$).

Table 1

Baseline demographics and clinical data for DCA and all other cardiomyopathy

Recipient Characteristic:	Dilated Anthracycline Cardiomyopathy (N=453)	All Other Cardiomyopathy (N=51,312)	<i>P</i> value
Age (median $\pm$ SD) (years)	44 $\pm$ 18	52 $\pm$ 19	<0.001 ^a
Female	66%	25%	<0.001 ^b
White	74%	76%	0.45 ^b
Weight (mean $\pm$ SD) (kg)	64 $\pm$ 20	72 $\pm$ 25	<0.001 ^a
Previous malignancy type			<0.001 ^b
Breast	24%	6%	
Leukemia	17%	7%	
Melanoma	0.3%	4%	
Other skin cancer	0.3%	7%	
Unknown/Other/Multiple	58%	76%	
Diabetes Mellitus	8%	9%	0.64 ^b
Cerebrovascular disease	3%	3%	0.78 ^b
Serum Creatinine (mean $\pm$ SD) (mg/dl)	1.23 $\pm$ 0.81	1.31 $\pm$ 1.24	<0.001 ^a
Panel Reactive Antibody (mean $\pm$ SD) (%)	5.8 $\pm$ 16.2	6.7 $\pm$ 18.2	0.79 ^a
Ischemic time (mean $\pm$ SD) (hours)	3.1 $\pm$ 1.0	3.1 $\pm$ 1.1	0.34 ^a
Left Ventricular Assist Device	13%	16%	0.0059 ^b
Medical Condition			0.012 ^b
Hospitalized	53%	56%	
Intensive Care Unit	17%	14%	
Intravenous Inotropes	48%	39%	<0.001 ^b
Peak Oxygen Consumption (ml/kg/min)	11.6 $\pm$ 3.7	11.7 $\pm$ 3.7	0.89 ^b
Mean Pulmonary Artery Pressure (mmHg)	30.6 $\pm$ 8.9	30.5 $\pm$ 10.7	0.42 ^a
Pulmonary Capillary Wedge Pressure (mmHg)	20.5 $\pm$ 7.9	20.9 $\pm$ 8.9	0.75 ^a
Cardiac Output (L/min)	3.6 $\pm$ 1.4	4.2 $\pm$ 1.4	<0.001 ^a

^aWilcoxon test;^bPearson test