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Cardiotoxicity In Hematologic Stem Cell Transplant: Keeping The Beat

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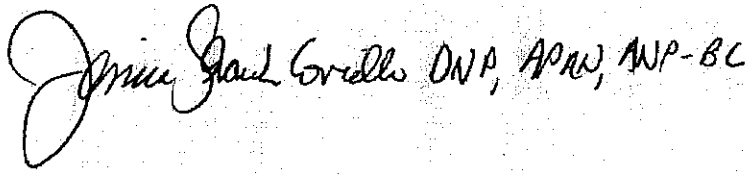

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Cardiotoxicity in Stem Cell Transplant: Keeping the Beat

Abstract

The number of hematopoietic stem cell transplants (HSCT) performed in the U.S. and worldwide is increasing. Cardiac events have been well described in HSCT, and incidence and type of cardiac events have not changed over recent decades. This study adds to the body of evidence in describing incidence and type of cardiac events experienced by an allogeneic and autologous HSCT population at one institution from 2012-2017. Sixty-five patients (9.8%) experienced cardiac events, including atrial arrhythmia (N = 39), acute heart failure (N = 9), acute coronary syndrome (N = 7), new onset hypertension (N = 9), with a few instances of bradycardia, ventricular arrhythmia, pericardial effusion, and pericarditis. Our multivariable regression analysis identified age (older), creatinine (higher) and history of coronary artery disease to significantly correlate with risk of cardiac event ($p = 0.005$, $p = 0.039$, $p = 0.038$ respectively). Patients developing a CE had an increased risk of death within one year (11% vs. 32%, $p < 0.001$). We review our results in context of other important HSCT cardiac studies to illuminate the most relevant factors of medical history, laboratory data, and cardiac measurements that will identify patients at higher risk, allowing for intervention to improve HSCT outcomes.

Introduction

The Surveillance, Epidemiology, and End Results Program data predict the hematologic malignancies of leukemia, lymphoma, and multiple myeloma to account for 9.7% of all diagnosed cancers in 2018 in the United States, translating to over 168,000 people diagnosed.[1] Many will be eligible for the treatment of hematopoietic stem cell transplant (HSCT). The availability of haploidentical transplant, improved supportive care for transplant recipients, and increasing enrollment in donor registry all contribute to an increased use of HSCT.[2,3] The Health Resources and Services Administration[4] calculates more than 22,000 HSCTs in the United States performed in 2016.

A substantial body of current literature examines cardiotoxicity (CT) in HSCT. Supplemental Tables 1 and 2 list many of these studies with incidence and type of CT, and positive and negative correlations of variables to cardiac risk. [5-25] Numerous studies recommend reducing cardiac related morbidity of transplant by identifying the at-risk subpopulation to target for intervention (Supplemental Table 3);[7-15,18-25] however, there is no uniform approach to evaluating cardiac risk for transplant candidates. Variability in HSCT and multiple factors determining cardiac risk preclude a cookie-cutter risk assessment tool. Clinicians can strive to individualize approach to care and reduce risk of cardiac events (CE) by optimizing diagnostic and therapeutic methods before, during, and after transplant.

The purpose of this study was to describe the incidence, type, and circumstances of CE that developed in a population of patients recently having undergone HSCT and explore potential risk

factors of CE. We examined our findings in conjunction with other pertinent studies to consider approaches to cardiac risk of HSCT patients.

Methods

The Yale Institutional Review Board granted approval to retrospectively analyze data from medical records of 660 patients who underwent HSCT at Yale New Haven Hospital from January
2012 through December 2017. We examined all 660 charts and identified patients that experienced a CE, defined as a cardiac complication that required medical intervention due to arrhythmia, function failure, significant blood pressure variant (with exception of hypotension associated with sepsis), or inflammatory condition of the heart. Any CE occurring from conditioning up to three months post-transplant was included. Charts of patients not experiencing a CE served as control group, for which we used a random sampling, aiming at a 1:3 case to control ratio for analysis. Charts from both groups were reviewed for demographic, diagnostic, and death data. Choice of variables to study was based on prior studies' findings (Supplemental Tables 1-3) and clinicians' experience and curiosity.

Demographics, past medical history, and diagnostic data are listed in Table 1. Serologic data were tracked at time points of pre-transplant, day of transplant, and time of CE. ECG measurements were recorded pre-transplant and time of CE. Diagnostic data also included review of pulmonary function tests (PFTs). Timing of CE and post-transplant complications of neutropenic fever, sepsis, engraftment syndrome, and fluid volume overload were noted. Use of cardiac medications and consumption of drugs with QTc interval prolonging potential were reviewed. Timing of deaths up to one-year post-transplant was collected.

Statistical Analysis

Study statistics were calculated to characterize patient demographics, clinical characteristics, and outcomes with mean [standard deviation (SD)], median [interquartile range (IQ)], or number (percentage). A two-sample t-test or Wilcoxon rank sum test was used in univariate analysis to compare continuous variables between patients with and without CE, while a Chi-square test or Fisher's exact test was used to compare categorical variables. Independent variables included into the multivariable logistic regression analysis of cardiac events were subject to a screening process that combined both statistical evidence (univariate p-value <0.1) and clinical evidence reported from literature. All statistical analyses were performed in software SAS version 9.4 (Cary, NC). A two-sided p-value of <0.05 was considered statistically significant.

Results

Sixty-five of 660 patients (9.8%) experienced cardiac events (Figure 1), and 183 patients without cardiac events were chosen as control (total 248 patients). Several of those 65 patients experienced more than one type of cardiac diagnosis, for a total of 80 events. Atrial arrhythmia (fibrillation or flutter) was the most common event (N=39, 49% of events). Of atrial arrhythmias, eight occurred during engraftment, of these, three occurred with a diagnosis of engraftment syndrome. Six developed while patients had a neutropenic fever, one during pancytopenia without fever, three during conditioning therapy.

Acute heart failure (AHF) was the second most common cardiac complication (N = 9, 11%). It was the first experience of HF for five patients. There were seven occurrences (9% of events) of acute coronary syndrome (ACS), six with demand ischemia associated with ST changes. Two of the ACS events developed during febrile neutropenia, one during engraftment, one in setting of

respiratory failure and pulmonary overload, one in setting of cocaine use. One patient had an MI on day 0, prior to stem cell infusion. Five patients developed pericardial effusions associated with other cardiac events, including two with pericarditis, one during hypertensive crisis, one during AHF. Three experienced pericarditis, one severe episode during conditioning therapy in a patient with T-cell lymphoma who received 1600 cGy mediastinal radiation, one viral pericarditis following recovery from transplant, one in setting of disease recurrence.

Hypertensive crisis and new onset HTN requiring continued medical therapy occurred in three and nine patients respectively. HTN was often associated with HF and volume overload or ACS. Symptomatic bradycardia developed in three patients, one with etoposide during conditioning, one following a hypertensive crisis, one during engraftment syndrome.

Most patients who experienced a CE (N = 65) did so post-transplant, Day +8 to +14 (N = 22/65 patients, 34%). Twelve patients (18%) developed an event during conditioning and 13 (20%) post-transplant Day +1 to +7. Two patients suffered events on Day 0, one prior to stem cell infusion and one following infusion. Seven patients (11%) had a CE Day +15 to +30 and nine patients (14%) from day +31 to day +90.

Univariate results for demographics, medical history, serologic, and diagnostic data are reported in Table 1. Multivariable regression analysis (Table 2) found three variables to independently associate with risk of experiencing CE: age (older), creatinine level before transplant (higher), and history of CAD. For every one-unit (5-year) increase in age, holding other variables at fixed values, one would expect a 27% increase in odds of developing CE (OR=1.27, 95% CI:1.081.50, p=0.005). One-unit (=0.2) difference in creatinine was significantly associated with increased

odds of developing CE (OR=1.14, 95% CI:1.01-1.30, p = 0.039). The odds of developing a CE for patients with CAD history was 3.82 times of those without (95% CI: 1.08-13.51, p = 0.038).

Atrial dilation was found by echocardiogram (TTE) in 28 of the 65 patients who experienced a CE and in 48 of the 183 patients who did not have a CE (p = 0.013). Subgroup analysis was performed to assess for association between atrial dilation and development of atrial fibrillation/flutter for the group of patients that did experience a CE (N = 65). There was a statistically significant association between having atrial dilation and experiencing atrial arrhythmia, with 21 of 27 (78%) patients with atrial dilation developing atrial arrhythmia, compared to 18 of 35 (51%) patients without dilation (p = 0.03).

Table 1 reports death outcomes and Table 3 lists deaths by primary cause within one year of transplant. More patients with CEs died within first three months of transplant compared to patients without CEs. Within one year of transplant, there were significantly more deaths in the CE than the non-CE group (p <0.001), including two additional cardiac-related deaths. Between 6 months and one year of HSCT, there were nine deaths in the non-CE group and eleven in the CE group.

Three cardiac-related deaths occurred within three months of transplant:

- 61-year-old man with recurrent follicular lymphoma, h/o HTN and Type II DM developed HF with volume overload, pulmonary edema, and respiratory failure leading to cardiac arrest day +65 of allogeneic transplant. Pre-transplant meds included ACEI, BB, and diuretic, pre-transplant BNP was 31,173, creatinine 1.27. TTE notable for trace mitral regurgitation and global strain of -14.

- 71-year-old man with AML, h/o HTN and HL, developed AHF in setting of reduced haplo-identical transplant. Received post-transplant Cytoxan which was felt to contribute to myocardial injury. Medications included ACEI and diuretic, TTE showed mild diastolic dysfunction, mild aortic and trace mitral regurgitation, pre-transplant creatinine 1.3.
- 58-year-old man undergoing autologous transplant with h/o CAD, HTN, HL, COPD, and cardiac stent placement six months prior to transplant suffered a cardiac arrhythmia with heart failure and died day +9 during engraftment. Medications included betablocker, pre-transplant MUGA did not show dysfunction, creatinine was 1.

The remaining four deaths in the CE group that were not cardiac-related included three deaths related to bacteremia/septic shock and one death due to idiopathic pneumonia syndrome. Three deaths occurred within three months of transplant in the non-cardiac event group, two due to bacteremia/septic shock and one progressive leukemia.

Discussion

The incidence of 9.8% and the types of CE found in this study (Figure 1) are consistent with other studies (Supplemental Tables 1 and 2). Consistent with several studies,[17,22-25] we found age to be an independent predictor of CE. While not surprising, it's important to note, as the Center for International Blood and Marrow Transplant Research[26] found over 50% of transplant recipients to be over the age of 60 in 2016, and over the age of 70 in 12% and 4.6% of autologous and allogeneic transplants respectively. Sorror's (2014) Comorbidity Age Index[27] calculates hazard ratios for non-relapse mortality to increase from 1.21 for those aged 40 to 49 years to 1.75 for those $\geq$ 60. However, Sorror concludes that age is a poor prognostic factor, and

outlines a composite measure to include comorbidities. Further, many HSCT studies do not identify age as independently prognostic of CE.[9,10,18,24,25] One study found that younger patients who had less cardiac reserve to be at higher mortality risk within three months of transplant, suggesting the importance of function over age.[28]

Our finding of increased risk of CE with higher creatinine levels is concordant with two similar studies.[6,18] Creatinine level as an indication of renal function may be an imperfect surrogate, as it may reflect hydration status, drug metabolism, and other acute disease states. However, the impact of kidney health on cardiovascular disease is well-established,[29,30] and as renal dysfunction will impact a patient's ability to tolerate conditioning treatments and their recovery from transplant, signs of even modest renal insufficiency should be incorporated into consideration of cardiac risk.

HF has been described as an oncogenic condition, and common pathways of inflammation and oxidative stress may lead to both cardiovascular disease and cancer.[31] An association has been found between the presence of clonal hematopoiesis of indeterminate potential (CHIP) and CAD[32,33]. Our finding of CAD correlating with increased risk of CE is consistent with several studies;[6,7,16,24,25] however, unlike some studies' whose focus was arrhythmia as a cardiotoxicity of transplant,[6,7,13,17,18] we did not find other cardiac history, including HTN, to correlate with risk. Family history of cardiac disease did not correlate with a CE, although accurate collection of this data, that is, whether no family history was known vs. no cardiac disease present, was unclear.

Pre-transplant ECGs are used to assess arrhythmias, QTc interval prolongation, and evidence of structural abnormalities. QTc prolongation may reflect preclinical cardiac injury, has arrhythmogenic potential, and causes provider anxiety for potential torsades de pointes. Literature review found one study correlating QTc prolongation with acute HF[21] and one to trend with increased non-relapse morbidity.[34] Like most studies looking at QTc,[7,9,10] we found no correlation with CE. Still, monitoring QTc during transplant may be useful: the average QTc found at time of CE was 469 with range revealing values at the upper limit of normal or modestly prolonged (450-508), suggesting that QTc may be helpful to alert clinicians as a sign of non-clinical cardiac stress. HSCT patients require use of drugs with QTc prolonging potential including antibiotics, antifungals, and antiemetics. At least one study suggests an increased risk of CT due to multiple QTc prolonging agents.[35] We found taking multiple (three or >) QTc prolonging medications to correlate with risk on univariate but not multivariable analysis. Of note, a few studies argue for using QTc dispersion as a better measure for evaluating cardiac risk[9,36]. Pre-transplant dispersion measurements may reflect subtle cardiac damage more accurately.

Left ventricular hypertrophy (LVH) and left ventricular ejection fraction (LVEF) are measures by imaging commonly studied to correlate with cardiac risk. Many studies lend support to the significance of EF and other imaging measurements to portend cardiac risk,[15,18,24,25,29,37] yet we know patients with modestly low EF reductions can safely undergo transplant,[26] and an EF value in isolation is often not found to correlate with a CE.[6,7,9,21] We found EF and LVH significant on univariate analysis, but neither on multivariable analysis. Advances in strain imaging by TTE

may prove to prognosticate well for cardiac dysfunction.[38,39] A global strain of <10.5 is known to increase a risk of CE in patients with HF, and has been shown to be more predictive of mortality than LVEF of mortality.[40] While we found global strain to correlate with CE on univariate analysis, strain was reported for only 37% of subjects and therefore not included in multivariable analysis. Consistent reporting and study of global strain will clarify its importance in predicting risk and identifying patients who require more sensitive MRI measurements.

Atrial arrhythmias are well described in the post-transplant setting.[6,7,12,13,16,18,23,24] In this study, 73% of all atrial arrhythmias occurred during autologous (rather than allogeneic) transplant. While atrial arrhythmias may herald less in the way of morbidity and mortality than other cardiac events, one should not discount its significance or become complacent in accepting its risk. We know that atrial arrhythmias increase patients' length of stay in hospital and can be associated with increased likelihood of ICU admission, in-hospital mortality, and death within one year.[6,13] Furthermore, persistent arrhythmia can increase risk of thrombus, require anticoagulation, and contribute to long-term cardiac dysfunction. We found pre-transplant atrial dilation by TTE in those that experienced a CE to correlate with incidence of atrial fibrillation, which has been noted in at least one other study.[18]

Clinicians have studied blood biomarkers to predict cardiac risk, including BNP, troponins, and lipid panels. BNP levels in the immediate post-transplant period can signal ventricular wall stress and have been shown to predict for later post-transplant CT, so may be useful to follow during transplant to gauge degree of cardiac stress.[11,23] However, pre-transplant BNP levels have not

been found to be specific for a CE,[15,41] and our study endorses this finding. One prospective study found BNP elevation early in transplant following fluid load to indicate relative protection from later CT.[15] Troponins may however be useful as a marker following CT chemotherapy to identify patients at risk for CE[39,42] or those who may benefit from cardio-protective agents.[43] On review of evidence of studies looking at HL and correlative risk of CE or increased mortality, two studies found a positive correlation[16,25] and one did not.[10] We found a history of HL to correlate with CE on univariate analysis, but not on multivariable, and there was insufficient data of lipid panels and use of cholesterol lowering agents to include for analysis.

Electrolyte imbalance may contribute to risk of arrhythmia. In this study, calcium was the only electrolyte that showed some correlation with CE on univariate analysis; however, calcium levels were not corrected for albumin levels. Subsequent evaluation of data showed that while patients with significant hypocalcemia did have low levels when adjusted, all had low albumin levels, which may be the true correlate, and is known to be associated with overall increased morbidity in other disease processes.[44] Electrolyte levels at the time of CE were not significantly low, and no other electrolyte correlations were found.

Almost all patients with diagnoses of leukemia or lymphoma in our study received anthracycline therapy; no independent correlation was found with exposure and CE. Current literature is discrepant in finding this variable predictive of a CE; our review found four studies to correlate,[10,12,24,45] and two not.[8,9] Anthracycline is a mainstay of therapy and will for the foreseeable future contribute to Type I (irreversible) CT, whereas improved therapeutic radiation techniques contribute much less cardiotoxicity than previously.[46] We did not find a correlation

with pre-transplant history of pulmonary disease, smoking status, or PFT measurements. Only 19 of the 248 patients (case and case control groups), 8%, were referred to the cardio-oncology service.

Our finding of more deaths in the first three months of transplant in the CE group is expected, as patients that experience serious complications that lead to death, such as sepsis, will be at higher risk for arrhythmias and heart failure. Those more susceptible to CE may carry comorbidities that likewise predispose them to other serious health complications, reflected here in a higher risk of death within one year.

Study Limitations

We included many variables to assess their correlations with cardiac risk, but additional potential factors such as albumin, hemoglobin, glucose, alcohol use, and psychological distress level were not collected. In addition, novel agents carry unique cardiotoxicities,[47-49] and their use in our patient population was not explored. Global strain and lipid levels couldn't be included in multivariable analysis due to the significant number of missing values. Our definition of CE was broad, and any CE occurring up to three months post-transplant was mixed together for analysis. Finally, this is a one institution retrospective study; findings aren't generalizable without being further validated with external data.

Conclusion

Our study finds age, renal dysfunction, and history of CAD to be important factors of cardiac risk in HSCT. We found an increased risk of death within one year of HSCT for those who experienced a CE. We suggest history of HL and DM and imaging measurements of EF, LVH, global strain, and presence of atrial dilation to consider in risk assessment, and suggest BNP,

troponin, and QTc intervals to be monitored for signs of cardiac stress before, during, and early post-transplant. Working with cardio-oncology colleagues, the at-risk population can be considered for cardio-protective agents, increased monitoring during transplant, and tighter control of comorbidities pre and post-transplant.[49-52]

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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Supplementary information is available at *Bone Marrow Transplantation's* website.

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Table 1

Summary statistics of demographic data, medical history, and diagnostic data

	No Cardiac Event Group N = 183	Percent	Cardiac Event Group N = 65	Percent	P value
Demographics					
Age	54 (12.84)		61 (9.29)		0.001
Gender					
Male	118	*64*	45	*69*	
Female	65	*36*	20	*31*	0.49
BMI	28.8 (6.19)		28.9 (5.37)		0.5
Active smoker	20	*11*	2	*3*	0.06
Past smoker	75	*41*	30	*46*	0.47
Conditioning therapy					
Ablative	135	*74*	40	*62*	
Reduced intensity	48	*26*	25	*38*	0.06
Transplant					
Autologous transplants	118	*64*	38	*58*	
Allogeneic transplants	65	*36*	27	*42*	0.39
Diagnosis*/% total cases*					
AML	26	*14*	10	*15*	0.82
ALL	10	*5*	7	*11*	0.16
MDS	4	*2*	1	*2*	1
Multiple Myeloma	57	*31*	24	*37*	0.41
Lymphoma	64	*35*	19	*29*	0.59
POEMS	1	*1*	1	*2*	0.46
Amyloid	3	*2*	0	*0*	0.57
Aplastic Anemia	1	*1*	2	***3***	0.17
Myeloproliferative disorder	3	*2*	0	*0*	0.57
CML/CMML	4	*2*	1	*2*	1
Germ Cell Tumor	5	*3*	0	*0*	0.33
BPDCN	1	*1*	0	*0*	1
Anthracycline exposure	104	*57*	31	*49*	0.2
Medical History					
h/o severe renal dysfunction	11	*6*	4	*24*	0.03
h/o coronary artery disease	6	*4*	9	*14*	0.005
h/o hypertension	62	*34*	36	*56*	0.002
h/o myocardial infarction	3	*2*	3	*5*	0.19
h/o stent placement	5	*3*	4	*6*	0.25

h/o heart failure	10	*5*	3	*5*	1
h/o atrial arrhythmia	7	*4*	7	*11*	0.06
h/o ventricular arrhythmia	2	*1*	0	*0*	1
h/o diabetes mellitus	15	*8*	12	*18*	0.02
h/o hyperlipidemia	37	*20*	21	*32*	0.048
h/o COPD	7	*4*	4	*6*	0.49
h/o asthma	8	*4*	4	*6*	0.52
Family h/o cardiac disease	81	*51*	30	*56*	0.56
h/o peripheral vascular disease	1	*0.5*	1	*2*	0.46
Lab Data					
Creatinine before transplant	0.96 (0.36)		1.17 (0.76)		0.04
Calcium level before transplant	8.92 (0.59)		8.78 (0.51)		0.09
Potassium level before transplant	3.77 (0.52)		3.74 (0.33)		0.88
Magnesium level before transplant	1.76 (0.22)		1.79 (0.23)		0.62
ProBNP level, before transplant	86.0 (41.0-176.8)		140.0 (65.7-427.0)		0.16
Cardiac Measurements					
QTC before transplant	440.21 (23.56)		447.57 (31.36)		0.09
Ejection fraction pre-transplant	60.59 (5.89)		60.11 (6.37)		0.59
Global strain*	-17.54 (2.72)		-16.37 (2.29)		0.017
Left ventricular hypertrophy	31	*17*	21	*32*	0.009
Atrial dilation	48	*27*	28	*44*	0.013
Diastolic dysfunction	59	*35*	22	*37*	0.91
Death Outcomes					
Death within 3 months of transplant	3	*2*	7	*11*	0.004
Death within 6 months of transplant	11	*6*	10	*15*	0.034
Death within 1 year of transplant	20	*11*	21	*32*	<0.001

Note: Data are presented as mean (SD), median (IQR), and n (*%*).

AML=acute myeloid leukemia; ALL=acute lymphoid leukemia; MDS=myelodysplasia; POEMS=polyneuropathy organomegaly endocrinopathy m-protein, skin changes syndrome; CML=chronic myeloid leukemia; CMML=chronic myelomonocytic leukemia; BPDCN=blastic plasmacytoid dendritic cell neoplasm

*Only 95 values available, 153 values missing (not measured)

Table 2

Multivariable logistic regression analysis of risk factors associated with developing cardiac event

Variables	**Odds Ratio (OR) (95%) CI)**	**P-value**
Age*	1.27 (1.08 - 1.50)	0.005
Creatinine before transplant**	1.14 (1.01 - 1.30)	0.039
Calcium before transplant	0.68 (0.49 - 1.13)	0.136
CAD, Yes	3.82 (1.08 - 13.51)	0.038
HTN, Yes	1.37 (0.70 - 2.67)	0.353
Diabetes, Yes	2.31 (0.95 - 5.65)	0.065
Hyperlipidemia, Yes	0.80 (0.37-1.75)	0.575

*One-unit increase = 5 years for age

** One-unit increase = 0.2 for creatinine

Table 3
All deaths within one year

	No Cardiac Event Group N = 183	Percent	Cardiac Event Group N = 65	Percent
Death related to progression of disease	13	*7%*	4	*6%*
Death related to infection	3	*2%*	10	*15%*
Death related to GVHD	2	*1%*	1	*2%*
Death related primarily to cardiac dysfunction	0	*0%*	5	*8%*
Unknown	2	*1%*	1	*2%*

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Figure 1

Cardiac Event Diagnoses