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Arrhythmias in the Setting of Hematopoietic Cell Transplants

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Abstract

Prior studies report 9–27% of persons receiving a hematopoietic cell transplant develop arrhythmias, but the effect on outcomes is largely unknown. We reviewed data from 1177 consecutive patients {greater than or equal to}40 years old receiving a hematopoietic cell transplant at one center during 1999–2009. Transplant indication was predominately leukemia, lymphoma and multiple myeloma. Overall, 104 patients were found to have clinically significant arrhythmia: 43 prior to and 61 following transplant. Post-transplant arrhythmias were most frequently atrial fibrillation(N=30), atrial flutter(N=7) and supraventricular tachycardia(N=11). Subjects with an arrhythmia post-transplant were more likely to have longer median hospital stays (32 days vs 23, P=<.001,) a greater probability of an ICU admission (52% vs 7%; P<.001), more inhospital deaths (28% vs 3%, P<0.001), and more deaths within one year of transplant (41% vs 15%; P<0.001) than patients without arrhythmia at any time. In a multivariate model including age at transplant, diagnosis, history of pre-transplant arrhythmia, and transplant-related variables, post-transplant arrhythmia was associated with a greater risk of death within a year of transplant (OR 3.5, 95% CI: 2.1, 5.9; P < 0.001). Our data suggest arrhythmias after transplants are associated with significant morbidity and mortality. A prospective study of arrhythmia in the transplant setting is warranted.

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Keywords

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INTRODUCTION

Hematopoietic cell transplant (HCT) offers cure for many specific hematologic conditions and malignancies.[1] Although achievements in treatment approach and supportive care have resulted in substantial improvements in overall survival and treatment-related mortality, survivors of HCT remain at risk for significant late effects of therapy, including premature death.[2–8] A recent report from the Bone Marrow Transplant Survivor Study cohort reported that two-thirds of HCT survivors will develop a chronic health condition; in over one-third, the condition will be severe, life-threatening, or fatal.[5]

Cardiovascular disease is among the most life-threatening of the potential late effects of HCT. Previous reports have described a range of HCT-related cardiotoxicity including valvular disease, pericardial effusion and pericarditis, hypertension, congestive heart failure, and cardiac arrhythmias.[7, 9–13] Prior studies report that the incidence of arrhythmias during autologous or allogeneic HCT is 9–27%.[14–19] With the increasing age of transplant recipients, the prevalence pre-HCT comorbidities, including arrhythmia, is likely to increase.[8, 20, 21] To date, few studies have examined the impact of arrhythmias that occur after transplant,[21–23] although limited data suggest that supraventricular arrhythmias are associated with transplant-related mortality.[24] Furthermore, pre-existing arrhythmias are included in calculations for the HCT-specific comorbidity index, which is used to risk stratify patients prior to transplant, but data on outcomes are limited.[25] Therefore, in an effort to better understand the impact of arrhythmia in the transplant setting, we conducted a single-center retrospective analysis of arrhythmia among patients undergoing HCT.

METHODS

Participants

Data collection and analysis were performed with the approval of the Institutional Review Board of Memorial Sloan-Kettering Cancer Center, New York, NY. Protected health information was coded in accordance with requirements of Health Insurance Portability and Accountability Act. Baseline demographic, clinical and laboratory data including history of pre-existing arrhythmias, cardiovascular risk factors, cancer diagnosis, and transplant characteristics, were collected by a retrospective review of the inpatient and outpatient medical records of all patients who underwent autologous or allogeneic HCT between January 1999 and August 2009 at Memorial Sloan-Kettering Cancer Center. Arrhythmia history and characteristics were confirmed by a cardiologist (WS or RS). Clinically-significant arrhythmia during transplant, as further defined below, was carefully noted. Records were also reviewed for length of hospital stay, ICU admission, in-hospital death, death at one year, and other clinical information. Because the pediatric and young adult population may differ with regards to treatment, risk factors, and outcomes after arrhythmia, only patients 40 years or older were included in the analysis. All care or screening was done

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on a clinical basis as indicated by the treating team. As such, all patients underwent a clinical assessment of cardiac function prior to transplant, including ekg and echocardiography or multiple gated cardiac blood pool imaging (MUGA). With few exceptions, patient had LV EF of ≥ 50% prior to transplantation. Stress tests were performed at the clinical discretion of the treating physician prior to transplantation.

Preparative regimens, donors and grafts

Regimens were identified as myeloablative, reduced intensity, and non-myeloablative as per previously described criteria.[26–28] Total body irradiation less than or equal to 500 cGy was considered reduced intensity; less than or equal to 200 cGy was considered non-myeloablative. Peripheral blood progenitor cell (PBPC) grafts for use in autologous HCT were generally obtained by administration of chemotherapy followed by granulocyte colony stimulating factor with apheresis on the 5^{th} and, if needed, the 6^{th} day. Transplants primarily used peripheral blood progenitor cells, but a small percentage of patients underwent bone marrow transplant. Donors for allogeneic HCT included matched/mismatched siblings or unrelated donors recruited via the National Marrow Donor Program. Slightly more than half of the grafts for allogeneic HCT were T cell depleted. Selection of CD34+ stem cells from PBSC grafts was accomplished using the ISOLEX 300i Magnetic Cell Separator, followed by sheep red blood cell (sRBC)-rosette depletion of T cells as previously described.[29] Bone marrow T cell depletion was accomplished by sequential soybean agglutination and sRBC-rosette depletion.[30] For T cell depleted grafts, no medicinal GVHD prophylaxis was given.

Arrhythmias and Cardiac Risk Factors

Manual review of each medical chart, including physician's notes, EKGs, Holter monitors, telemetry, echocardiography, MUGAs, and stress tests, was performed by a board-certified cardiologist (WS). Clinically-significant arrhythmia was defined as paroxysmal or chronic atrial fibrillation, supraventricular tachycardia, ventricular tachycardia or fibrillation. Isolated ectopy, including ventricular premature contractions, atrial premature contractions, and other clinically insignificant arrhythmias, such as those noted on telemetry and those that did not require a change in management were not included in the definition of clinically-significant. Major cardiovascular risk factors were identified, including essential hypertension, hypercholesterolemia, diabetes mellitus, and past or present tobacco use.

Statistics

T-test (for continuous variables), Fisher's exact test (for categorical variables), and multivariable regression models were used to compare length of hospital stay, ICU admission, in-hospital death, and death at one year among patients with a history of arrhythmia prior to transplant (pre-existing arrhythmia) to those without a history of arrhythmia. In addition, patients without pre-existing arrhythmias who experienced new arrhythmia during transplant were compared to those who did not have arrhythmia at any time. Stepwise mutivariable logistic regression, testing age, gender, traditional cardiovascular risk factors (hypertension, hypercholesterolemia, smoking), diagnosis of diabetes mellitus, established (known) coronary artery disease, and transplant-related variables, was performed. P values less than 0.05 were considered significant. All statistical analyses were performed using STATA (Stata corporation, College Station, Texas).

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RESULTS

Overall

Eleven hundred seventy-seven patients underwent a total of 1255 HCTs; 446 (36%) allogeneic and 809 (64%) autologous (Table 1). Patients were majority male (60%), with a median age of 56 years (range, 40 to 76 years). Approximately one third had a history of hypertension (404; 34%). The most common pre-transplant diagnosis was lymphoma (427; 36%), followed by multiple myeloma (326; 28%) and leukemia (234; 20%). Forty-three patients were found to have arrhythmia documented prior to HCT; an additional 61 experienced an arrhythmia during transplant. The most common type of arrhythmia was atrial fibrillation (30, 49%), followed by supraventricular tachycardia (11, 18%) and atrial flutter (7, 11%). Only two patients (3%) experienced nonsustained ventricular tachycardia.

Patients with pre-existing arrhythmias

Among the patients who experienced arrhythmia prior to HCT (N=43), atrial fibrillation was the most prevalent arrhythmia (32, 74%), followed by supraventricular tachycardia (3, 9%) and atrial flutter (2, 5%). One patient had a history of ventricular tachycardia. Patients with pre-HCT arrhythmias were older than those without (62 years old vs 56 years old, P <0.001), but were equally distributed between male and female (Table 2). Cancer diagnoses were not significantly different in patients with pre-HCT arrhythmias compared to those without. The incidence of cardiac risk factors, including smoking, hypertension, diabetes or hypercholesterolemia, was similar in those with pre-HCT arrhythmias as in those without, although patients with pre-HCT arrhythmias were more slightly more likely to have established coronary artery disease (5% vs 1%, P= 0.06).

History of pre-HCT arrhythmia did not have an apparent impact on transplant parameters. As noted, transplants were predominantly performed with peripheral blood progenitor cell (PBPC) grafts (N=1143) with no significant difference in grafts between patients with pre-HCT arrhythmias and those without (6% vs 97%, P = 0.4). Also, there was no significant difference between the two groups with respect to the type of transplant (autologous transplant, 55% vs 65%, P =0.2) or the conditioning regimen (myeloablative, 75% vs non-myeloablative or reduced intensity, 85%, P = 0.09). T-cell depletion was performed in approximately half of the allogeneic HCTs in both groups (50% vs 52%, P = 0.9), in keeping with standard practice patterns at this institution. Anti-thymocyte globulin (ATG) was administered in more than half of the allogeneic HCTs, with no significant difference between the patients with pre-HCT arrhythmia (60.0%) and those without (53%, P = 0.6).

Patients with pre-HCT arrhythmias were more likely to experience an arrhythmia during transplant, compared to patients without a history of arrhythmia (39% vs 5%, P <0.001) (Table 2). Patients with pre-HCT arrhythmia were also more likely to be admitted to the ICU (23 vs 10%, P = 0.009) and had longer median hospital stays (26 vs 23 days, P = 0.04). Both in-hospital death and death within one year of transplant were also more frequent in patients with pre-HCT arrhythmias (23% vs 4% P =<0.001 and 37% vs 16%, P <0.001, respectively).

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Arrhythmias during transplant

Sixty-one patients (5%) experienced new arrhythmia during of following HCT, predominantly atrial fibrillation, atrial flutter or supraventricular tachycardias. Compared to patients who had no history of arrhythmia and did not experience arrhythmia during HCT (N=1073), patients who experienced post-HCT arrhythmias were older (median age 56 vs 58 years, $P = 0.023$), but were not more likely to be male or to have known cardiovascular disease or risk factors (smoking, hypertension, diabetes, hypercholesterolemia, established coronary artery disease) (Table 2).

Patients undergoing bone marrow transplant (BMT) were more likely to have post-HCT arrhythmia than patients undergoing PBPC transplants (16% vs 5%, $P = 0.009$), though the number of patients undergoing BMT was small (N = 32). Arrhythmias were observed equally in patients receiving myeloablative vs reduced intensity or non-myeloablative HCTs combined (5% vs 7%, P = 0.4). Patients undergoing allogeneic HCTs (N=738) were significantly more likely to experience post-HCT arrhythmias compared to patients receiving autologous (N = 396) HCTs (8% v 4%, $P = 0.001$). Post-HCT arrhythmias occurred somewhat more often in T cell depleted (N=218) compared to conventional HCTs (N=916) (9% vs 4%; $P = 0.01$). In addition, there was a slightly higher incidence of post-HCT arrhythmias among patients receiving ATG (N=214) as part of their treatment compared to patients who did not (N=920) (9% vs 4%, $P = 0.001$).

Patients without a history of arrhythmia who experienced an arrhythmia during HCT (N=61) had poorer outcomes compared to patients who did not experience arrhythmia prior to or during transplant (N=1073; Table 2). Patients with first arrhythmia following HCT, compared to those without any arrhythmia, were more likely to have an ICU admission (52% vs 7%, $P <.001$), longer mean hospital stays (32 days vs 23, $P = <.001$) increased in-hospital mortality (28% vs 3%, $P <0.001$) and death within one year of transplantation (41% vs 15%, $P <0.001$); (Table 2). Post-HCT arrhythmia was also associated with allogeneic, rather than autologous, stem cell transplant (OR 3.5, 95%CI: 2.5 to 4.8; $P < 0.001$), while patients with a history of multiple myeloma had a slightly decreased risk for post-HCT arrhythmia (OR 0.4, 95% CI: 0.2, 0.9; $P = 0.01$).

In a multivariate model including age at transplant, diagnosis, pre-transplant arrhythmia, receipt of ATG, receipt of T-cell depleted stem cells, type of graft (BMT versus PBPC), and type of transplant (allogeneic versus autologous), only allogeneic transplant (OR 4.3, 95 CI: 28, 6.6; P < 0.001) and post-HCT arrhythmia (OR 3.5, 95% CI: 2.1, 5.9; $P < 0.001$) retained an association with death at one year. When overall mortality during the study period was examined, post-HCT arrhythmia (OR 2.5, 95% CI: 1.5, 4.1; $P < 0.001$), allogeneic transplant (OR 3.6, 95% CI: 2.4, 5.3; P < 0.001) and arrhythmia prior to transplant (OR 2.7, 95% CI: 1.4, 5.4; P = 0.003) were all found to be significant in a multivariate model including age, diagnosis, receipt of ATG, type of graft, and receipt of T-cell depleted stem cells.

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DISCUSSION

In this large single-center retrospective study, arrhythmias, whether occurring prior to HCT or first occurring after transplant, were associated with poor clinical outcomes including longer hospital stays and increased mortality.

Patients with arrhythmia prior to transplant (pre-HCT arrhythmia) were more likely to experience an arrhythmia during transplant, compared to those who did not have an arrhythmia prior to transplant. Patients with pre-HCT arrhythmia were older and more frequently had pre-existing coronary artery disease.[31] Importantly, although the most common pre-HCT arrhythmia was atrial fibrillation, a history of pre-HCT arrhythmia correlated with a two-fold increase in the risk of ICU admission, a 5-fold increase in the risk of in-hospital death and a two-fold increase in the risk of death at one year. In sum, these findings suggest that pre-HCT arrhythmias, including atrial fibrillation, are of significant clinical importance.

Among patients with no history of arrhythmia, arrhythmias after HCT were a poor prognostic indicator. Patients with a new arrhythmia after transplant had an 8-fold increase in risk of ICU admission, a 9-fold increase in risk for in-hospital death and a 3-fold increase in risk for death within one year of transplant. Notably, this single-center study found a lower prevalence of arrhythmias following transplant than prior reports[20, 21, 32], possibly due to the relative youth of the patients in this analysis.

Arrhythmias were more common among patients who received BMT, as compared to PBPC, and among those who received T cell-depleted, compared to conventional grafts. To our knowledge, these observations have not been previously reported in the literature. While some of these associations may be due to underlying illness not fully accounted for in the multivariate model, these associations could be further explored in a prospective setting.

Certain limitations of our findings should be noted. First and foremost, these results do not support an assertion that arrhythmia caused the observed adverse outcomes, and should be interpreted with that caveat. That said, only those arrhythmias that required a change in management or a treatment decision were highlighted for this study, and many patients were cared for without telemetry monitoring. This study, like others, is also limited by single-institution retrospective data, although this series is the largest reported to date. Single-institution medical records ensured that pre-transplant records could be reviewed in a systematic and thorough fashion, and chart details could be verified, when required. Finally, differences in electrolyte abnormalities, individual chemotherapy agents (such as melphalan), or receipt of calcineurin inhibitors were not included in this retrospective review; prospective studies may consider collecting these data for analysis.

With the limitations in mind, our findings continue to suggest that clinical attention to arrhythmias in the transplant setting is warranted. Atrial arrhythmias in the setting of transplantation may be similar to atrial arrhythmias in the post-operative setting, where the risks of increased length of stay, morbidity and mortality have been firmly established.[33–35] Since the recognition of atrial arrhythmias as a harbinger of poor outcomes in the surgical setting, a robust literature on early intervention and treatment algorithms has emerged,[33–35]

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although none exists for arrhythmia in the transplant setting. This gap in the literature opens the way for possible prophylactic, diagnostic and therapeutic interventions with respect to arrhythmias during transplantation. Furthermore, no prospective analysis has examined treatment algorithms for arrhythmia in the transplant setting. However a paper from Fatema and colleagues suggests that improved fluid management may be beneficial.[32] Echocardiographic measures, including left atrial volume and diastolic parameters, may help identify patients without known arrhythmias who are at risk.[36] Following brain natruretic peptide (BNP) or more widespread use of telemetry monitoring may be helpful.[32] Finally, prophylaxis with agents such as amiodarone, and treatment with early cardioversion, or aggressive rate control may also offer benefit.[37, 38]

In conclusion, in this analysis of 1178 patients undergoing HCT, a small but significant number of primarily supraventricular arrhythmias were noted. This manuscript is among the first to report that arrhythmia after transplant correlated strongly with adverse outcomes, including risks of ICU admission, in-hospital death and death within one year of transplant. Notably, causation cannot be concluded; it is unclear whether arrhythmias are simply markers of poorer outcomes in gravely ill patients or mechanistically contribute to the adverse outcomes. The small number of patients at each transplant center who experience arrhythmias will continue to limit our understanding and hamper development of diagnostic, prophylactic and treatment algorithms. Prospective, multicenter studies employing resources such as the Center for International Blood and Marrow Transplant Research (CIBMTR) are needed.

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Summary

We evaluated cardiac arrhythmia among 1177 consecutive patients ≥40 years old undergoing hematopoietic cell transplant. 104 patients had arrhythmia, primarily supra-ventricular. Development of a new arrhythmia was associated with poorer outcomes including death within one year of transplant.

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Table 1

Characteristics of 1177 patients undergoing hematopoietic cell transplantation.

Number, total	1177
Male (N, %)	701 (60%)
Age at transplant in years (Median, Range)	56 (40–76)
Hypertension (N, %)	404 (34%)
Diabetes mellitus (N, %)	112 (10%)
Current smoker (N, %)	501 (43%)
Coronary artery disease (N, %)	69 (6%)
Diagnosis pre-transplant:	
Lymphoma (N, %)	427 (36%)
Multiple myeloma (N, %)	326 (28%)
Leukemia (N, %)	234 (20%)
Myelodysplastic syndrome (N, %)	70 (6%)
Other (N, %)	120 (10%)
Conditioning regimen:	
Total body irradiation alone (N, %)	25 (2%)
Total body irradiation plus chemotherapy (N, %)	50 (4%)
Other chemotherapy combinations (N, %)	1102 (94%)
Allogeneic transplant only (N, %)	416 (35%)
Died within one year of transplant (N, %)	200 (17%)

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Table 2

Patients undergoing hematopoietic cell transplantation with pre-existing arrhythmia, arrhythmia during transplant, and without arrhythmia.

	Pre-transplant arrhythmia	Without pre-transplant arrhythmia	*P*	Arrhythmia during transplant	No arrhythmia	*P*
Number, total	43	1134		61	1073	
Male (N, %)	28 (56)	673(57)	0.449	31 (51)	642 (60)	0.163
Median age at transplant, in years	62	56 (5)	0.000	58	56	0.023
Hypertension (N, %)	20 (47)	385 (34)	0.165	20 (33)	365 (34)	0.844
Diabetes mellitus (N, %)	6 (14)	106 (9)	0.312	7 (11)	99 (9)	0.557
Current smoker (N, %)	23 (53)	479 (42)	0.245	29 (2)	450 (42)	0.389
Coronary artery disease (N, %)	7 (16)	62 (5)	0.063	4 (7)	58 (5)	0.700
Diagnosis pre-transplant:						
Lymphoma (N, %)	14 (33)	413 (36)	0.605	20 (33)	393 (37)	0.544
Multiple myeloma (N, %)	12 (28)	315 (28)	0.752	9 (15)	306 (29)	0.020
Leukemia (N, %)	10 (23)	212 (19)	0.572	18 (30)	206 (19)	0.049
Myelodysplastic syndrome (N, %)	5 (12)	65 (6)	0.109	4 (7)	61 (6)	0.776
Other (N, %)	3 (7)	117 (10)	0.392	10 (16)	107 (10)	0.982
Conditioning regimen:						
TBI* alone (N, %)	1 (2)	24 (2)	0.892	2 (3)	22 (2)	0.517
TBI* plus chemotherapy (N, %)	1 (2)	50 (4)	0.449	5 (8)	45 (4)	0.139
Other chemotherapy combinations (N, %)	6 (14)	1095 (97)	0.316	54 (89)	1006 (94)	0.108
Allogeneic transplant only (N, %)	20 (47)	396 (35)	0.119	33 (54)	363 (34)	0.001
Arrhythmia during transplant (N, %)	17 (40)	61 (6)	<0.001	-	-	
ICU admission (N, %)	10 (23)	108 (10)	0.003	32 (52)	76 (7)	<.001
In-hospital death (N, %)	10 (23)	50 (4)	<0.001	17 (28)	33(3)	<.001
Length of stay, median (days)	26	23	0.04	32	23	<.001
Death within one year of transplant (N, %)	16 (37)	184 (16)	<0.001	25 (41)	159 (15%)	<.001

* TBI: Total body irradiation