Melphalan-Induced Supraventricular Tachycardia: Incidence and Risk Factors

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ABSTRACT

Background: Cardiotoxicity of aggressive chemotherapeutic regimens includes cardiomyopathy and arrhythmias. Although cardiomyopathy is a well-recognized entity, arrhythmias are poorly studied.
Hypothesis: Certain chemotherapeutic regimes are associated with supraventricular arrhythmias, particularly atrial fibrillation.
Methods: We retrospectively reviewed the data on patients who received hematopoietic stem cell transplant (bone marrow transplant; BMT) from 1998 to 2005 and developed supraventricular tachycardia (SVT) during the same hospital admission. The Fisher χ^2 test and the Student *t* test were used for comparison of categorical and continuous variables, respectively.
Results: During the period of 1998–2005, there were 1221 BMTs, 62 (5.1%) of which were complicated by SVT. Melphalan-based regimens demonstrated a significantly higher rate of SVT than any other chemotherapy. Out of 438 patients who received melphalan, 48 (11%) developed atrial fibrillation (n = 35) or SVT (n = 13) during the same hospital admission, and 390 did not. Patients with SVT were older, had higher baseline creatinine, larger size of the left atrium, and more cardiac comorbidities. Incidence of SVT was associated with greater length of stay (24.9 ± 8.9 d vs 19.6 ± 5.8 days, $P < 0.0001$), even after adjustment for comorbidities.
Conclusions: Supraventricular tachycardia, mostly atrial fibrillation, complicates about 5% of chemotherapeutic treatments used with BMT. Melphalan is the most arrhythmogenic agent, and is associated with SVT in 11% of patients. Development of SVT results in about a 4-day increase in the length of hospital stay.

Introduction

With growing use of chemotherapy, cardiotoxicity is increasingly recognized as a common side effect. Although chemotherapy-induced cardiomyopathy is well-described, the arrhythmogenic potential of different chemotherapeutic regimens is poorly studied. Meanwhile, for cardiologists working in cancer centers, atrial fibrillation (AF) is one of the most frequent reasons for consults. The aim of this retrospective study is to compare the rate of proarrhythmic effects of commonly used cancer drugs, and to identify the risk factors and clinical impact of resulting arrhythmias.

Methods

We retrospectively reviewed the data from the bone marrow transplant (BMT) department at the H. Lee Moffitt Cancer Center to identify patients who received hematopoietic stem cell transplant (BMT) from 1998 to 2005, and specifically those who had "rhythm disorder" listed as a complication. Dates of admission, BMT, arrhythmia, and discharge were recorded for each patient. Patient demographic and clinical characteristics including weight, height, systolic and diastolic blood pressures, heart rate, maximal temperature, and laboratory values of white blood cell count, hematocrit, creatinine, potassium, and magnesium serum levels were collected for the day of BMT and the day of arrhythmia. Only patients who were in sinus rhythm on admission were included. The mean time from BMT to arrhythmia was 7 days. Therefore, for patients without arrhythmia, clinical and laboratory data were collected on the seventh day after BMT.

We collected information of all different chemotherapeutic conditioning regimens used in each patient. We then reviewed progress notes and, when available, rhythm strips and electrocardiograms to identify the type of arrhythmia. Data regarding comorbidities including hypertension, diabetes, and coronary artery disease, as well as history of myocardial infarction, AF, and congestive heart failure, were collected. Echocardiographic parameters from the echoes performed within 3 months of the procedure, including left ventricular ejection fraction (LVEF), left atrial size, severity of mitral regurgitation, and pulmonary artery systolic pressure, were collected when available.

The proportion of patients with new onset of supraventricular tachycardia (SVT)—which included AF, atrial flutter,

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atrioventricular node reentrant tachycardia, or atrial tachycardias, but excluded sinus tachycardia—was compared based on the drug regimen, with subsequent comparison of those who developed SVT and those who did not.

Statistical Analysis

Linear regression analysis was used to identify predictors of SVT. After initial univariate analysis, adjustments were made for major confounders, specifically patient age and cardiovascular comorbidities. The Fisher χ^2 test and Student t test were used for comparison of categorical and continuous variables, respectively. A P value <0.05 was considered significant. All statistical analysis was performed using SPSS, version 17.1 (SPSS Inc., Chicago, IL).

Results

From 1998 to 2005, there were 1221 BMTs at the Moffitt Cancer Center, 26.9% allogenic and 72.1% autologous. The median age of the patients was 50.2 years (range, 18 to 77.4 years). Gender distribution was even, with 52.5% women and 47.5% men. Of the patients, 80.75% were white, 7.21% black, and 7.8% Hispanic. Multiple myeloma was the indication for 34.23% of all BMTs, followed by non-Hodgkin lymphoma (17.5%), breast cancer (14.82%), and Hodgkin lymphoma (6.06%).

Among these patients given chemotherapy with the BMT, 62 (5.1%) were complicated by SVT. Different chemotherapy regimens were associated with different rates of SVT (Table 1). Whereas in most regimens the rate of SVT did not exceed 2%, melphalan-based regimens demonstrated a significantly higher rate of SVT than any other chemotherapy.

Out of 438 patients who received melphalan, 48 (11%) developed AF or flutter (n = 35), or other SVT (n = 13) such as atrial tachycardia (n = 9) or atrioventricular node reentrant tachycardia (n = 4) during the same hospital admission, and 390 did not. The rate of SVT after melphalan was higher than after any other treatment ($P < 0.05$).

In patients with SVT, the most common malignancy was multiple myeloma (72.58%), followed by non-Hodgkin lymphoma (14.52%) and amyloidosis (4.84%). Similarly, most of the patients who developed SVT after melphalan treatment had multiple myeloma (91.6%). It reflected the distribution of pathology for which melphalan was used. In 359 of 390 (92.0%) patients who were on melphalan but did not develop SVT, the primary diagnosis was also multiple myeloma.

By linear regression analysis, the predictors of SVT were patient age, cardiovascular comorbidities (composite of hypertension, coronary artery disease, congestive heart failure, and diabetes), left atrial size, and creatinine on the day of arrhythmia.

Demographic, clinical, laboratory, and echocardiographic characteristics of patients with and without SVT following melphalan treatment are presented in Table 2. Patients with SVT were older (62.8 ± 7.9 y vs 55.5 ± 10.2 y, $P < 0.001$). Cardiovascular comorbidities were associated with a higher rate of SVT (52.1% vs 31.3%, $P < 0.01$). History of AF was present in 14 out of 48 patients who developed SVT and in 5 out of 390 patients who did not (29.2% vs 1.3%, $P < 0.001$). Serum creatinine was higher (1.4 ± 1.5 mg/dL vs 1.0 ± 1.2 mg/dL, ($P = 0.027$) in those with SVT on the day of the arrhythmia. Size of the left atrium was greater (3.9 ± 0.5 cm vs 3.1 ± 0.7 cm, $P < 0.001$) in patients with SVT. Left ventricular ejection fraction, pulmonary artery systolic pressure estimated by velocity of tricuspid regurgitation, and dose of melphalan were similar in patients with and without SVT. Surprisingly, SVT was associated with higher potassium level on the day of arrhythmia (4.4 ± 0.5 mg/dL vs 3.7 ± 0.4 mg/dL, $P = 0.03$).

All 48 patients who developed SVT on melphalan had a normal LVEF (61 ± 9%). The only abnormal parameter was left atrial enlargement in 15 patients out of 48.

Presence of arrhythmias prolonged the length of hospital stay, which was greater in those who developed SVT (24.9 ± 8.9 d vs 19.6 ± 5.8 d, $P < 0.0001$), even after adjustment for comorbidities and age (Table 3).

Table 1. Rate of SVT in Different Chemotherapeutic Regimens

Chemotherapeutic Agent	N	SVT	%	*P* Value
Busulfan	248	5	2.0	NS
Melphalan	438	48	11.0	<0.05
Cyclophosphamide	580	11	1.9	NS
Fludarabin	91	0	0.0	NS
Carmustine	175	3	1.7	NS
Carboplatin	164	1	0.6	NS

Abbreviations: NS, not significant; SVT, supraventricular tachycardia.

Table 2. Baseline Characteristics of Patients on Melphalan With and Without SVT

	SVT		No SVT		
Characteristics	N	%	N	%	*P* Value
	48	100	390	100	
Female	27	56.3	174	44.6	NS
Male	21	43.8	216	55.4	NS
White	42	87.5	322	82.5	NS
Age (y)	62.9 ± 7.9		55.5 ± 0.2		<0.0001
Black	4	8.3	33	8.5	NS
Hispanic	2	4.2	35	9.0	NS
HT	25	52.1	122	31.3	<0.01
DM	4	8.3	23	5.9	NS
CAD	3	6.3	10	2.6	NS
Hemodialysis	4	8.3	9	2.3	NS
History of AF	14	29.2	5	1.3	<0.001

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; DM, diabetes mellitus; HT, hypertension; NS, not significant; SVT, supraventricular tachycardia.

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Table 3. Comparison of Patients on Melphalan With and Without SVT

	SVT	No SVT	
	48	390	
N	Mean ± SD	Mean ± SD	*P* Value
Baseline			
Left atrial size (cm)	3.9 ± 0.53	3.1 ± 0.7	<0.0001
LVEF (%)	61.3 ± 9.3	61.1 ± 6.3	NS
Pulmonary artery pressure (mm Hg)	49.8 ± 14.5	40.4 ± 6.8	NS
Systolic BP (mm Hg)	129.3 ± 17.9	128.1 ± 17.6	NS
Diastolic BP (mm Hg)	67.9 ± 11.8	68.4 ± 12.3	NS
T max, °C	36.9 ± 0.5	37.1 ± 3.6	NS
HCT	29.7 ± 3.1	29.9 ± 3.7	NS
Cr (mg/dL)	1.4 ± 1.5	1.1 ± 1.2	NS
WBC	3.8 ± 2.8	4.5 ± 3.3	NS
Potassium (mg/dL)	4.4 ± 0.5	4.3 ± 0.4	NS
On day of arrhythmia			
Systolic BP (mm Hg)	122.3 ± 21.7	122.8 ± 21	NS
Diastolic BP (mm Hg)	64.5 ± 12.1	68.3 ± 14.3	NS
T max, °C	37.8 ± 1.09	37.6 ± 1.1	NS
HCT	29 ± 4.3	30 ± 5.3	NS
Cr (mg/dL)	1.4 ± 1.5	1.0 ± 1.2	0.027
WBC	3.1 ± 4.2	3.7 ± 6.7	NS
Potassium (mg/dL)	3.7 ± 0.4	4.7 ± 9.7	0.03
Melphalan dose (mg/m²)	189.4 ± 21	187.5 ± 22.4	NS
LOS, unadjusted (d)	24.9 ± 8.9	19.6 ± 5.8	<0.0001
LOS, adjusted for comorbidities (d)	23.7 ± 5.2	19.4 ± 5.5	<0.0001

Abbreviations: BP, blood pressure; Cr, creatinine; HCT, hematocrit; LOS, length of stay; LVEF; left ventricular ejection fraction; NS, not significant; SD, standard deviation; SVT, supraventricular tachycardia; T max, maximum temperature; WBC, white blood cells.

Discussion

In this retrospective study, we demonstrated that AF and SVT occur in about 5% of BMT recipients. Melphalan was the most arrhythmogenic of all chemotherapeutic agents, causing SVT in 11% of patients, especially in elderly patients with cardiovascular comorbidities. We also demonstrated an association between renal dysfunction and chemotherapy-induced arrhythmias. To our knowledge, this is the largest cohort of patients receiving BMT in general, and melphalan in particular, specifically studied for arrhythmias.

The literature on chemotherapy-induced arrhythmia is scarce. We summarized it in our review published earlier.[1] Atrial fibrillation is a known complication of melphalan. Several authors have reported comparable but somewhat lower incidence of this arrhythmia after melphalan.

Olivieri et al[2] described AF in 5 of 76 (6.6%) patients receiving melphalan for BMT. A matched control group had no cases of arrhythmias. Four of the 5 patients subsequently had normal echocardiograms (including the presence of normal left atrial size) and exercise treadmill tests. Two of them needed repeat therapy with melphalan and had no recurrence of AF while being maintained on prophylactic propafenone. Moreau et al[3] documented 2 patients (7.4%) who experienced reversible paroxysmal AF after treatment with high-dose melphalan. In a cohort study by Sirohi et al,[4] AF occurred at the same rate (2 of 17 patients) in younger and in older patients. In our experience, the elderly, not unexpectedly, were more prone to SVT. Among patients age >60 years, Mileshkin et al observed AF in 9 out of the 40 patients.[5] In another study to determine maximal tolerable dose and dose-limiting toxicity of melphalan, 8.3% of patients with multiple myeloma had AF after receiving high-dose therapy (>280 mg/m^2).[6]

The mechanism of AF and SVT after melphalan is not very clear. Melphalan is an oral cell-cycle phase nonspecific alkylating agent used in the treatment of multiple myeloma; breast, testicular, and ovarian cancers; non-Hodgkin lymphoma; and osteogenic sarcoma. It is often used prior to BMT. In reality, melphalan, most commonly used in combination with other drugs, has a strong cardiotoxic potential, as it has been reported to cause left ventricular (LV) dysfunction in up to 15% of patients treated prior to allogenic stem cell transplantation. Pericardial disease, a powerful trigger of AF, has also been observed during melphalan therapy,[7] and it is likely that this condition is more frequent than clinically recognized.[8] In summary, the model of triggers, represented by direct or indirect chemotherapy-mediated cardiac injury, acting on an atrial substrate, rendered more predisposed to develop AF by preexisting pathologies, seems to explain satisfactorily our observation of increased incidence of this arrhythmia following melphalan administration.

We did not find any occurrence of LV dysfunction in our study. All patients had baseline LVEF in the normal range. The only exception was a patient who had an LVEF of 15% during AF, but he was not receiving melphalan. It is likely that patients with decreased LVEF were screened out before chemotherapy. Because it was not a prospective trial, echocardiograms were not obtained after chemotherapy. There were no cases of clinical heart failure, but asymptomatic LV dysfunction easily could have been missed.

Renal dysfunction as a confounder of SVT after melphalan was never reported before. The pharmacokinetics of melphalan suggest that renal function is correlated with both the elimination rate constant and area under the curve of oral melphalan.[9] The Clinical Cancer and Leukemia Group B study also suggested an increased toxicity of intravenous melphalan in patients with renal dysfunction.[10] It may be possible that the increased frequency of atrial arrhythmias in patients with renal dysfunction in our study is a manifestation of the above-mentioned phenomenon. Surprisingly, in our study a higher total dose of melphalan was not associated with higher incidence of SVT.

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In general, the link between atrial arrhythmias and kidney insufficiency is poorly established. Recently, several studies found higher prevalence of AF in chronic kidney disease. In the Chronic Renal Insufficiency cohort, almost 20% of patients had AF, which was 2×–3× higher than in general population.[11] An inverse relationship of glomerular filtration rate and AF was reported by Iguchi et al.[12] Also, there is an association of renal impairment and AF in elderly people.[13] The link between decreased kidney function and AF, combined with impaired clearance of melphalan, can possibly explain higher creatinine in our cohort with melphalan-induced atrial arrhythmias.

Study Limitations

This a retrospective study performed in an oncology facility with focus on cardiac data, which is usually not the primary interest of treating physicians. Many patients who developed arrhythmias were not on telemetry, and the data on the duration and hemodynamic parameters of arrhythmia are missing. Echocardiograms were not routinely performed after treatment, which could result in missed cases of chemotherapy-induced cardiomyopathy.

Conclusion

In our study, atrial arrhythmias, mostly AF, complicated about 5% of chemotherapeutic treatments used with BMT. Melphalan is the most arrhythmogenic agent, associated with atrial arrhythmias in 11% of patients. Atrial arrhythmias are more common in patients with increased age and concomitant cardiovascular comorbidities. Some well-established risk factors, such as age and left atrial size, as well as previously unknown factors like kidney insufficiency, are linked to atrial arrhythmias. Because atrial tachycardia and AF after melphalan results in about a 4-day increase in hospital stay, patients on melphalan need to be monitored for arrhythmias. Targeting these high-risk patients with preventive treatment should be considered, and this can be further studied in a prospective randomized controlled fashion with a variety of rate- and rhythm-control medications.

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