Biol Blood Marrow Transplant 25 (2019) 2261–2266

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Venous Thromboembolism in Autologous Blood or Marrow Transplantation Survivors: A Report from the Blood or Marrow Transplant Survivor Study

Radhika Gangaraju[1,*], Yanjun Chen[1], Lindsey Hageman[1], Jessica Wu[1], Liton Francisco[1], Kevin Battles[1], Michelle Kung[1], Emily Ness[1], Mariel Parman[1], Daniel J. Weisdorf[2], Stephen J. Forman[3], Mukta Arora[2], Saro H. Armenian[3], Smita Bhatia[1]

[1] *Institute for Cancer Outcomes and Survivorship, University of Alabama at Birmingham, Birmingham, Alabama*
[2] *Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, Minnesota*
[3] *Pediatric Hematology/Oncology, City of Hope, Duarte, California*

Article history:
Received 24 April 2019
Accepted 27 June 2019

Keywords:
Venous thromboembolism
BMT survivors
Autologous BMT
Plasma cell dyscrasia

A B S T R A C T

Hemostatic complications are commonly encountered in blood or marrow transplantation (BMT) recipients, increasing their morbidity and mortality and are well described in the immediate post-transplantation period. The risk of venous thromboembolism (VTE) in long-term survivors of autologous BMT has not been studied previously. Patients who underwent autologous BMT between January 1, 1974, and December 31, 2010 for a hematologic malignancy, lived 2 years or more after transplantation, and were age ≥18 years were surveyed for long-term outcomes. The median duration of follow-up was 9.8 years (interquartile range, 6.4 to 14.3 years). We analyzed the risk of VTE in 820 autologous BMT recipients who survived for ≥2 years, compared with 644 siblings. BMT survivors were at a 2.6-fold higher risk of VTE compared with siblings (95% confidence interval [CI], 1.6 to 4.4; P =.0004), after adjusting for sociodemographic characteristics. Conditional on surviving for ≥2 years after BMT, the mean cumulative incidence of VTE was 3.9 ± .8% at 5 years and 6.1 ± 1.1% at 10 years. A diagnosis of plasma cell disorder (hazard ratio [HR], 2.37; 95% CI, 1.3 to 4.2; P = .004) and annual household income ≤$50,000 (HR, 2.02; 95% CI, 1.2 to 3.6; P = .015) were associated with increased VTE risk. Our data indicate that autologous BMT survivors are at elevated risk for developing late-occurring VTE. The development of risk prediction models to identify autologous BMT survivors at greatest risk for VTE and thromboprophylaxis may help decrease the morbidity and mortality associated with VTE.

INTRODUCTION

Blood or marrow transplantation (BMT) is associated with an acquired hypercoagulable state characterized by inflammation, endothelial damage and activation of endothelium-dependent coagulation factors, increased von Willebrand factor and platelet adhesion, increased thrombin generation, and decreased levels of anticoagulant proteins, such as antithrombin and protein C [1–3]. Previous reports of venous thromboembolism (VTE) in BMT recipients focused on the early post-transplantation period, with a widely variable incidence (.5% to 23.5%) depending on the population characteristics and the methods used for diagnosing VTE [4]. The majority of these studies are limited by brief post-BMT follow-up and/or relatively small samples [5]. Catheter-related thrombosis occurs frequently in patients with lymphoma and myeloma undergoing autologous BMT, and majority of these events occur within first 100 days post-transplantation [6]. A comprehensive assessment of the incidence and risk factors for VTE in long-term autologous BMT survivors has not been published to date, however. Such an assessment is important, given that VTE is associated with decreased survival in BMT recipients [7]. In the present study, we addressed this gap using the resources offered by the Blood or Marrow Transplant Survivor Study (BMTSS).

METHODS

The BMTSS is a collaborative effort between the City of Hope, University of Minnesota, and University of Alabama at Birmingham to examine long-term outcomes of individuals who have lived 2 years or longer after undergoing BMT between 1974 and 2010 at 1 of these 3 institutions. Comparison with a noncancer population has been made possible by asking participating survivors to invite a nearest-age sibling to the study. The Human Subjects Committees at the participating institutions approved the study protocol, and each participant provided informed consent in accordance with the Declaration of Helsinki.

Financial disclosure: See Acknowledgments on page 2266.

* Correspondence and reprint requests: Radhika Gangaraju, MD, Department of Medicine, University of Alabama at Birmingham, 1600 7th Avenue South, Lowder 500, Birmingham, AL 35233.
E-mail address: rgangaraju@uabmc.edu (R. Gangaraju).

https://doi.org/10.1016/j.bbmt.2019.06.032
1083-8791/

Table 1
Demographic and Clinical Characteristics of the Autologous BMT Survivors and Their Siblings

Variable	BMT Survivors		Siblings		*P* Value
	Number	%	Number	%	
VTE					
Yes	60	7.3	19	3.0	.0002
Sex					
Male	441	53.8	259	40.2	<.0001
Race/ethnicity					
White	648	79.0	552	85.7	.0004
Hispanic	71	8.7	49	7.6	
Asian	32	3.9	23	3.6	
Black	54	6.6	13	2.0	
Other	15	1.8	7	1.1	
Education					
High school or less	158	19.3	80	12.4	.0007
Some college	293	35.7	227	35.3	
College graduate	367	44.8	336	52.2	
Missing	2	.2	1	.2	
Household income					
≤$50,000	250	30.5	126	19.6	<.0001
$50,000-$100,000	247	30.1	200	31.1	
>$100,000	232	28.3	252	39.2	
Missing	91	11.1	66	10.3	
Health insurance					
Yes	804	98.1	628	97.5	.4885
History of smoking (ever)					
Yes	326	39.8	204	31.7	.001
Diabetes					
Yes	140	17.1	50	7.8	<.0001
Hypertension					
Yes	354	43.2	190	29.5	<.0001
Dyslipidemia					
Yes	312	38.1	147	22.8	<.0001
Female hormone replacement					
Yes	101	12.3	106	16.5	.02
Testosterone replacement					
Yes	138	16.8	28	4.4	<.0001
Primary diagnosis					
AML/MDS	95	11.6			
CML	9	1.1			
NHL	420	51.2			
PCD	296	36.1			
Stem cell source					
PBSCs	781	95.2			
Bone marrow	39	4.8			
Conditioning regimen					
Busulfan	76	9.3			
Carmustine	198	24.2			
Cytoxan	443	54.0			
Etoposide	449	54.8			
Melphalan	376	45.9			
Other	112	13.7			
Any radiation	362	44.2			
Relapse/SMN					
Yes	117	14.27			

AML indicates acute myeloid leukemia; MDS, myelodysplastic syndrome; CML, chronic myelogenous leukemia; NHL, non-Hodgkin lymphoma; GVHD, graft-versus-host disease; PBSCs, peripheral blood stem cells; SMN, subsequent malignant neoplasms.

A BMTSS survey was administered to eligible patients and covered the following: diagnosis by a healthcare provider of specific chronic health conditions, relapse of primary cancer and development of subsequent neoplasms, age at diagnosis of these health conditions, medication use, height and weight at the time of survey completion, and sociodemographic characteristics (sex, race/ethnicity, education, employment, household income, and health insurance) [8]. We have previously shown that BMT survivors are able to report their outcomes with a high degree of accuracy [9]. Information regarding primary cancer diagnosis, transplantation preparative regimens, and graft type (bone marrow or peripheral blood stem cells) was obtained from institutional databases.

In this study, we aimed to describe the risk of VTE in long-term autologous BMT survivors. We hypothesized that the risk of VTE will be high several years after BMT due to endothelial damage from previous treatments, including chemotherapy and radiation, a continued inflammatory state, and new-onset comorbidities in this patient population. Patients who were alive and age ≥18 years at the time of the study were included. The underlying hematologic malignancies included acute myeloid leukemia/myelodysplastic syndrome, chronic myelogenous leukemia, plasma cell disorder (PCD), and non-Hodgkin lymphoma. We excluded patients who underwent a second BMT. Self-report of VTE diagnosed by a healthcare provider was used to identify patients with VTE. Arterial thrombosis and thrombotic microangiopathy were not included as VTE outcomes.

A total of 1556 patients had undergone autologous BMT for hematologic malignancies at the City of Hope, University of Minnesota, and University of Alabama at Birmingham between 1974 and 2010, survived ≥2 years, were 18 years or older, and alive at study participation. Of these, 119 (7.6%) were lost to follow-up. Of the 1437 BMT recipients approached, 455 did not participate (185 [11.8%] refused participation and 270 [17.3%] did not respond to the survey request), yielding 982 participants (68.3% participation rate). Among the 982 study participants, 109 did not have an available history of VTE. Because we were interested in studying the risk of post-BMT VTE, patients who developed VTE before BMT or with missing age at VTE diagnosis were excluded (n = 53). After these exclusions, a total of 820 patients were included in the final analysis.

Statistical Analysis

Logistic regression was used to study the risk of VTE in BMT survivors compared with their siblings, adjusting for age at study participation, sex, race/ethnicity, education, annual household income, insurance, body mass index (BMI), and comorbidities. Cumulative incidence of VTE conditional on surviving for ≥2 years after BMT was calculated using competing risk methods. Because we were interested in studying the risk of VTE in BMT recipients who survived for ≥2 years after BMT, we took 2 years after transplantation as the starting point to calculate the cumulative incidence. If the date of onset of VTE occurred within the first 2 years after BMT, the condition was considered as present 2 years after BMT. For the purpose of our analysis, the onset date was shifted forward to that time point. Data on long-term complications in cancer survivors have been presented in a similar way in previous publications [8,10]. Cox regression analysis was used to identify predictors of VTE risk among autologous BMT survivors [11]. Risk factors evaluated for association with VTE included age at BMT, sex, race/ethnicity, education, income, insurance status, BMI, primary hematologic malignancy, stem cell source, dyslipidemia, hypertension, diabetes, smoking, and hormone replacement therapy. Relapse of primary hematologic malignancy and development of subsequent neoplasms were analyzed as time-varying variables. Parsimonious models were obtained using backward variable selection, retaining variables with $P < .10$ in the model. Two-sided tests with $P < .05$ were considered statistically significant. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Demographic and clinical characteristics of the BMTSS cohort and their siblings are summarized in Table 1. The mean age at the time of BMT was 49.5 years (standard deviation ±12.6 years), whereas the mean age at survey participation was 60.5 ± 10.6 years for BMT survivors, compared with 53.1 ± 12.6 years in siblings. The cohort included 441 males (53.8%) and 648 non-Hispanic whites (79%). The median duration of follow-up after BMT was 9.8 years (interquartile range, 6.4 to 14.3 years). Primary diagnoses included non-Hodgkin lymphoma in 420 patients (51.2%), PCD in 296 (36.1%), acute myeloid leukemia/myelodysplastic syndrome in 95 (11.6%), and chronic myelogenous leukemia in 9 (1.1%). The majority of patients (781; 95.2%) were transplanted with peripheral blood stem cells. Cyclophosphamide was used as part of conditioning in 443 patients (54%), etoposide in 449 (54.8%), melphalan in 376 (45.9%), and total body irradiation (TBI) in 362 (44.2%). One hundred and seventeen

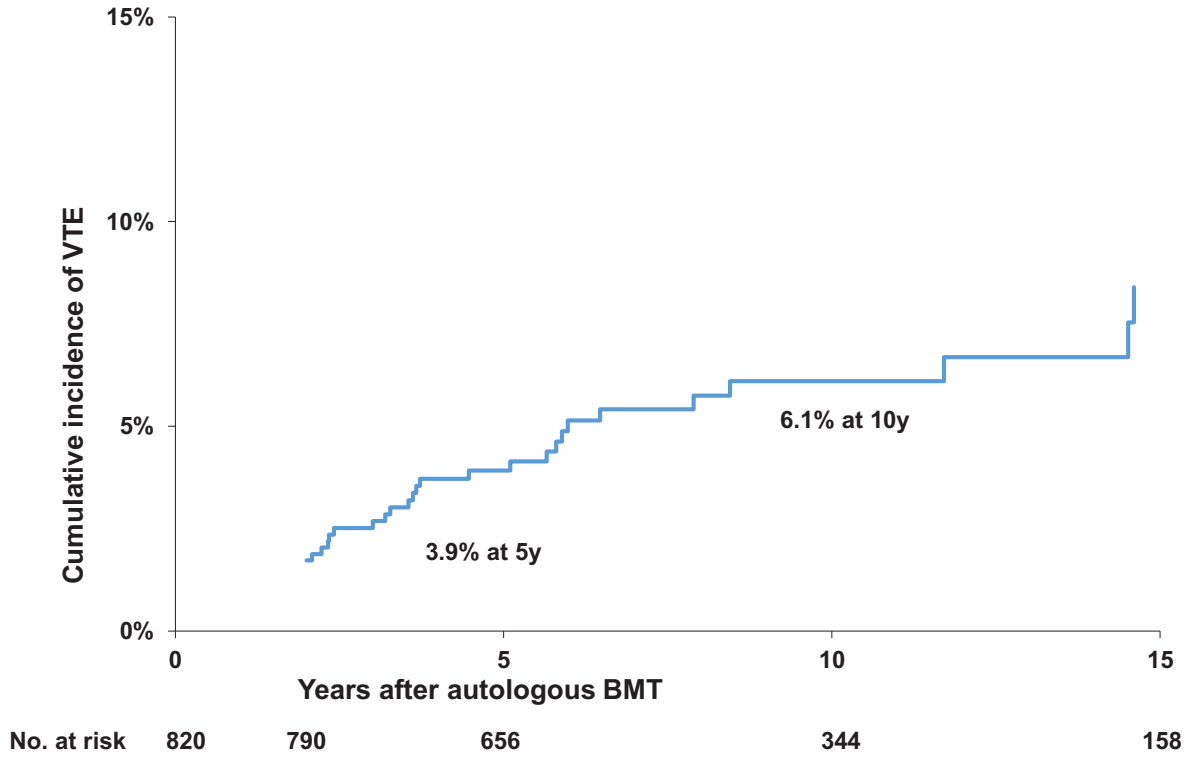

Figure 1. Cumulative incidence of VTE in autologous BMT survivors.

patients (14.3%) developed a subsequent malignancy or relapse of primary cancer post-BMT. Sixty patients (7.3%) developed VTE after BMT, 50% at ≥2 years after BMT. The median time to the development of VTE was 2.04 years from the time of BMT (interquartile range, 2.0 to 6.22 years). Conditional on surviving for ≥2 years after BMT, the cumulative incidence of VTE was 3.9 ± 0.8% at 5 years and 6.1 ± 1.1% at 10 years (Figure 1).

Risk of VTE in BMT Survivors versus Siblings

Logistic regression analysis after adjusting for age, sex, socioeconomic status, health insurance, comorbidities (ie, diabetes, hypertension, dyslipidemia, and BMI), smoking, and hormone replacement therapy showed that the odds of developing a VTE were significantly higher in BMT survivors compared with their siblings (odds ratio, 2.62; 95% confidence interval [CI], 1.55 to 4.43; $P = .0004$) (Table 2).

Risk of VTE among Autologous BMT Survivors

A diagnosis of PCD (hazard ratio [HR], 2.37; 95% CI, 1.3 to 4.2; $P = .004$) and annual household income ≤$50,000 (HR, 2.02; 95% CI, 1.2 to 3.6; $P = .015$) were associated with increased risk of VTE (Table 3).

DISCUSSION

We found a 2.6-fold higher risk of VTE in among autologous BMT survivors compared with a sibling cohort without cancer. Conditional on surviving for ≥2 years after BMT, the 10-year cumulative incidence of VTE was 6.1% after autologous BMT. These findings provide evidence of the need for ongoing vigilance regarding this complication.

Long-term BMT survivors are at increased risk of developing atherosclerosis, arterial vascular events, and new-onset cardiovascular risk factors, such as diabetes, hypertension, and dyslipidemia [12,13]. There had been a paucity of information regarding the risk of VTE among long-term autologous BMT survivors; our study is the first to address this issue. We found that an underlying diagnosis of PCD and low income were associated with an increased risk of VTE. Previous studies have shown that patients with PCD are at increased risk for VTE, due to either the primary

Table 2
Risk of VTE in Autologous BMT Survivors Compared with a Sibling Cohort

Variable	Univariate			Multivariate			Parsimonious*		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Cohort									
Siblings	1.00								
BMT cohort	2.60	1.5-4.4	.000	2.37	1.4-4.2	.003	**2.62**	**1.6-4.4**	**.0004**
Age at survey	1.02	1.0-1.1	.021	1.01	1.0-1.0	.221			
BMI	.99	1.0-1.0	.525	.98	.9-1.0	.375			
Sex									
Female	1.00								
Male	1.19	.8-1.9	.455	1.06	.6-1.8	.834			
Race/ethnicity									
Other	1.00			1.00					
Non-Hispanic white	1.38	.7-2.7	.331	1.45	.7-2.9	.288			
Education									
High school or less	1.00			1.00					
Some college	1.30	.6-2.7	.490	1.54	.7-3.3	.266			
College graduate	1.41	.7-2.9	.340	1.84	.9-3.9	.114			
Household income									
≤$50,000	1.00			1.00					
>$50,000	.69	.4-1.1	.133	.66	.4-1.1	.122			
Missing	.43	.2-1.1	.085	.41	.2-1.1	.080			
Health insurance									
Yes	.56	.1-4.2	.571	.61	.1-4.7	.631			
History of smoking									
Yes	1.14	.7-1.8	.590	1.01	.6-1.7	.954			
Diabetes									
Yes	1.34	.7-2.5	.345	1.25	.6-2.5	.512			
Hypertension									
Yes	1.30	.8-2.1	.267	1.21	.7-2.0	.467			
Hyperlipidemia									
Yes	1.01	.6-1.7	.954	.80	.5-1.4	.403			
Female hormone replacement									
Yes	.87	.4-1.7	.698	.91	.4-1.9	.791			
Testosterone replacement									
Yes	1.28	.7-2.5	.457	.98	.5-2.0	.951			

OR indicates odds ratio.
Values in bold type are statistically significant.
* The parsimonious model was obtained using backward variable selection, retaining variables with $P < .10$ in the model.

Table 3
Risk Factors for VTE in Autologous BMT Survivors

Category	Univariate			Multivariate			Parsimonious*		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Sex									
Female	1.00			1.00					
Male	.99	.6-1.6	.96	0.99	.6-1.8	.96			
Race/ethnicity									
Other	1.00			1.00					
White	1.42	.7-2.9	.34	1.41	.7-3.0	.36			
Age at diagnosis	1.01	1.0-1.0	.20						
Age at BMT	1.02	1.0-1.0	.06	1.01	1.0-1.0	.28			
BMI	.98	.9-1.03	.34	0.96	.9-1.0	.08	.96	.9-1.0	.10
Education									
High school or less	1.00			1.00					
Some college	1.09	.5-2.4	.83	1.25	.6-2.8	.60	1.25	.6-2.8	.59
College graduate	1.59	.8-3.3	.22	2.08	.9-4.6	.07	2.04	.9-4.5	.07
Household income									
>$50,000	1.00			1.00					
≤$50,000	1.60	1.0-2.7	.08	1.91	1.1-3.4	.029	**2.02**	**1.2-3.6**	**.015**
Missing	.31	.1-1.03	.06	.27	.1-.9	.036	.27	.1-.9	.03
Health insurance									
Yes	.92	.1-6.6	.93	.87	.1-6.5	.89			
Ever smoked									
Yes	1.03	.6-1.7	.92	1.08	.6-1.9)	.77			
Diabetes									
Yes	1.23	.7-2.3	.52	1.45	.7-2.9	.30			
Hypertension									
Yes	1.19	.7-2.0	.50	1.21	.7-2.1	.50			
Hyperlipidemia									
Yes	.74	.4-1.3	.27	.72	.4-1.3	.27			
Female hormone replacement									
Yes	.84	.4-1.9	.67	.78	.3-1.9	.58			
Testosterone replacement									
Yes	.78	.4-1.6	.48	.84	.4-1.8	.66			
Primary diagnosis									
NHL	1.00			1.00					
AML/MDS	1.51	.7-3.3	.30	1.82	.8-4.2	.15	1.58	.7-3.5	.26
CML	1.49	.2-11.1	.70	1.76	.2-14.0	.59	1.50	.2-11.3	.69
PCD	2.25	1.3-4.0	.005	2.04	1.1-3.7	.02	**2.37**	**1.3-4.2**	**.004**
Stem cell source									
Bone marrow	1.00			1.00					
PBSCs	1.51	.5-4.9	.49	1.34	.4-4.8	.65			
Relapse/SMN									
No	1.00			1.00					
Yes	.93	.8-4.9	.16	1.96	.8-5.0	.17			

SMN indicates secondary malignant neoplasms.
Values in bold type are statistically significant.
* The parsimonious model was obtained using backward variable selection, retaining variables with $P < .10$ in the model.

disease or treatment [14]. Multiple mechanisms, such as clonality; inhibition of natural anticoagulants or hypercoagulability due to inflammatory cytokines; increased von Willebrand factor, factor VIII, and fibrinogen levels; decreased protein S levels; acquired activated protein C resistance; and interference of fibrin structure by paraprotein, may contribute to this increased risk [15,16]. This risk increases by several fold in patients treated with thalidomide, lenalidomide, or pomalidomide in combination with high-dose dexamethasone, doxorubicin, or multiagent chemotherapy and in patients with ≥2 individual or PCD risk factors, and thromboprophylaxis is recommended in these patients [15]. Owing to the increased risk, several clinical trials have added thromboprophylaxis to the induction regimens of patients with multiple myeloma, with a subsequent decrease in VTE incidence [17,18]. Our study shows that the risk of VTE remains elevated several years after autologous BMT in patients with PCD. Some of these patients are likely being treated with maintenance therapies, which may contribute to continued increased risk of VTE after BMT. We were unable to abstract the post-transplantation maintenance therapy for patients with myeloma in our study and could not assess this as a risk factor for VTE. Thus, the increased risk of VTE in patients with PCD could be related to post-

transplantation exposure to maintenance therapy or the underlying diagnosis of PCD, or a combination of the two. The increasing use of post-transplantation maintenance therapy with lenalidomide in the current era may add to the risk of VTE after autologous BMT in patients with PCD. It is important to thoroughly investigate the risk factors and identify high-risk patients with PCD who may benefit from thromboprophylaxis after BMT, and this should be explored further in prospective studies.

Relapse of primary cancer or development of second malignancy was not associated with an increased risk of VTE. Comorbidities such as diabetes, hypertension, dyslipidemia, obesity, history of smoking, and use of oral contraception and hormonal therapy are known to contribute to the risk of VTE in the general population [19–21]; however, they were not associated with VTE risk in the autologous BMT survivors in our study. Given the increasing recognition of the link between clonal hematopoiesis of indeterminate potential and cardiovascular disease, studying the association between this disorder and VTE is an important topic for future studies.

The association between socioeconomic status and arterial cardiovascular disease is well established. A large population-based study from The Netherlands found an association between high neighborhood socioeconomic status and a lower risk of first VTE [22]. In another prospective study from Sweden, low income and lower educational level were independently associated with an increased risk of VTE [23]. It is possible that access to health care, physical activity, and general health awareness are lower in BMT survivors with low socioeconomic status and may be contributing to the increased risk of VTE.

Our study needs to be considered in the context of its limitations. First, the study relied on self-report to identify patients with VTE. However, previous evaluations of the validity of the BMTSS questionnaire have shown that survivors are able to report the occurrence of adverse medical conditions with accuracy [9]. Second, because our study was based on patient surveys, we could not capture complete details regarding clinical presentation and laboratory abnormalities at the time of VTE development. Future studies aimed at identifying biomarkers associated with VTE risk in BMT recipients are warranted. Although some patients provided details regarding the site of VTE, this information was not available for several patients, and thus we were not able to categorize the findings based on the site of VTE. Third, we did not have information regarding family history of VTE, level of physical activity, corticosteroid use, and hospitalizations at the time of VTE development. Fourth, the risk of VTE in BMT recipients was conditional on surviving the first 2 years after BMT. BMT recipients who died within the first 2 years were not included in the analysis, likely resulting in an underestimation of VTE risk after BMT. The incidence of VTE in the peritransplantation period is likely higher than what we found in our study patients, as a significant number of patients with VTE may have died within the first 2 years after transplantation. Our intention was to determine the risk of VTE in long-term BMT survivors. We found that this risk remains high several years after transplantation, necessitating continued risk assessment in these patients. These limitations notwithstanding, our study provides a comprehensive analysis of the long-term risk of VTE in autologous BMT recipients and the associated risk factors.

In conclusion, autologous BMT survivors have a 2.6-fold higher risk of VTE compared with their siblings without cancer. The risk continues to increase for at least 10 years after BMT. Patients with PCD and lower socioeconomic status are at particularly high risk. In light of these observations, it is important to delve further in identifying vulnerable subpopulations among patients with PCD treated with autologous BMT who may benefit from thromboprophylaxis.

ACKNOWLEDGMENTS

Financial disclosure: This study was supported in part by grants from the National Cancer Institute (R01 CA078938 and U01 CA213140) and the Leukemia and Lymphoma Society (R6502-16) (to S.B.).

Conflict of interest statement: There are no conflicts of interest to report.

REFERENCES

1. Kaufman PA, Jones RB, Greenberg CS, Peters WP. Autologous bone marrow transplantation and factor XII, factor VII, and protein C deficiencies. Report of a new association and its possible relationship to endothelial cell injury. *Cancer*. 1990;66:515–521.
2. Verheij M, Dewit LG, Boomgaard MN, Brinkman HJ, van Mourik JA. Ionizing radiation enhances platelet adhesion to the extracellular matrix of human endothelial cells by an increase in the release of von Willebrand factor. *Radiat Res*. 1994;137:202–207.
3. Vannucchi AM, Rafanelli D, Longo G, et al. Early hemostatic alterations following bone marrow transplantation: a prospective study. *Haematologica*. 1994;79:519–525.
4. Zahid MF, Murad MH, Litzow MR, et al. Venous thromboembolism following hematopoietic stem cell transplantation—a systematic review and meta-analysis. *Ann Hematol*. 2016;95:1457–1464.
5. Gonsalves A, Carrier M, Wells PS, McDiarmid SA, Huebsch LB, Allan DS. Incidence of symptomatic venous thromboembolism following hematopoietic stem cell transplantation. *J Thromb Haemost*. 2008;6:1468–1473.
6. Hegerova L, Bachan A, Cao Q, et al. Catheter-related thrombosis in patients with lymphoma or myeloma undergoing autologous stem cell transplantation. *Biol Blood Marrow Transplant*. 2018;24:e20–e25.
7. Gangaraju R, Chen Y, Hageman L, et al. Late mortality in blood or marrow transplant survivors with venous thromboembolism: report from the Blood or Marrow Transplant Survivor Study. *Br J Haematol*. 2019;186:367-370.
8. Sun CL, Francisco L, Kawashima T, et al. Prevalence and predictors of chronic health conditions after hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor Study. *Blood*. 2010;116:3129–3139. [quiz: 3377].
9. Louie AD, Robison LL, Bogue M, Hyde S, Forman SJ, Bhatia S. Validation of self-reported complications by bone marrow transplantation survivors. *Bone Marrow Transplant*. 2000;25:1191–1196.
10. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006;355:1572–1582.
11. Cox DR. Regression models and life-tables. *J R Stat Soc Series B Stat Methodol.*. 1972;34:187–220.
12. Baker KS, Ness KK, Steinberger J, et al. Diabetes, hypertension, and cardiovascular events in survivors of hematopoietic cell transplantation: a report from the Bone Marrow Transplantation Survivor Study. *Blood*. 2007;109:1765–1772.
13. Bhatia S. Long-term health impacts of hematopoietic stem cell transplantation inform recommendations for follow-up. *Expert Rev Hematol*. 2011;4:437–452. [quiz: 453-454].
14. Falanga A, Marchetti M. Venous thromboembolism in the hematologic malignancies. *J Clin Oncol*. 2009;27:4848–4857.
15. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia*. 2008;22:414–423.
16. Leebeek FW. Update of thrombosis in multiple myeloma. *Thromb Res*. 2016;140(suppl 1):S76–S80.
17. Cavo M, Zamagni E, Tosi P, et al. First-line therapy with thalidomide and dexamethasone in preparation for autologous stem cell transplantation for multiple myeloma. *Haematologica*. 2004;89:826–831.
18. Baz R, Li L, Kottke-Marchant K, et al. The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline-based chemotherapy for multiple myeloma. *Mayo Clin Proc*. 2005;80:1568–1574.
19. Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. *Circulation*. 2008;117:93–102.
20. Grady D, Hulley SB, Furberg C. Venous thromboembolic events associated with hormone replacement therapy. *JAMA*. 1997;278:477.
21. Beyer-Westendorf J, Bauersachs R, Hach-Wunderle V, Zotz RB, Rott H. Sex hormones and venous thromboembolism—from contraception to hormone replacement therapy. *Vasa*. 2018;47:441–450.
22. Kort D, van Rein N, van der Meer FJM, et al. Relationship between neighborhood socioeconomic status and venous thromboembolism: results from a population-based study. *J Thromb Haemost*. 2017;15:2352–2360.
23. Isma N, Merlo J, Ohlsson H, Svensson PJ, Lindblad B, Gottsäter A. Socioeconomic factors and concomitant diseases are related to the risk for venous thromboembolism during long time follow-up. *J Thromb Thrombolysis*. 2013;36:58–64.