ARTICLE

Venous thromboembolism is associated with graft-*versus*-host disease and increased non-relapse mortality after allogeneic hematopoietic stem cell transplantation

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Haematologica 2017
Volume 102(7):1185-1191

ABSTRACT

Although venous thromboembolism rates and risk factors are well described in patients with cancer, there are limited data on the incidence, risk factors and outcomes of thrombosis after allogeneic stem cell transplantation, a curative therapy for patients with hematologic malignancies. We aimed to determine the incidence and risks associated with venous thrombosis in allogeneic stem cell transplants. We studied 2276 recipients of first transplant between 2002-2013 at our institution with a median follow up of 50 months (range 4-146). Using pharmacy records and subsequent chart reviews, 190 patients who received systemic anticoagulation for venous thrombosis were identified. The 1- and 2-year cumulative incidence of all venous thrombotic events were 5.5% (95% confidence interval (CI) 4.6-6.5%) and 7.1% (95% CI 6.1-8.2%), respectively. There was no difference in age, sex, body mass index, diagnosis, disease risk index, conditioning intensity, donor type or graft source between transplant recipients with and without subsequent thrombosis. In multivariable models, both acute and chronic graft-*versus*-host disease were independently associated with thrombosis occurrence (Hazard ratio (HR)=2.05, 95% CI 1.52-2.76; HR=1.71, 95% CI 1.19-2.46, respectively). Upper extremity thrombosis differed from all other thromboses in terms of timing, risk factors and clinical impact, and was not associated with non-relapse mortality (HR=1.15; 95% CI 0.69-1.90), unlike all other thromboses which did increase non-relapse mortality (HR=1.71; 95% CI 1.17-2.49). In subgroup analysis evaluating conventional thrombosis predictors by comparing patients with and without thrombosis, a history of prior venous thrombosis was the only significant predictor. Venous thromboembolism has a high incidence after allogeneic stem cell transplant and is associated with graft-*versus*-host disease and non-relapse mortality.

Introduction

The care of patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT), a curative modality for advanced/aggressive hematologic malignancies, is highly complex, involving central venous catheters, conditioning chemotherapy, immune suppressive therapies for prophylaxis and treatment of graft-*versus*-host disease (GvHD), donor graft infusions, and infection monitoring and treatment. Their medical acuity and complexity makes allogeneic HSCT recipients

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Received: January 11, 2017.
Accepted: March 17, 2017.
Pre-published: March 24, 2017.

doi:10.3324/haematol.2017.164012

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: www.haematologica.org/content/102/7/1185

potentially vulnerable to venous thromboembolism (VTE) despite eradication of the underlying malignancy, but this complication remains incompletely characterized. Studies in autologous HSCT recipients have described a VTE incidence between 3% and 23.5%[1-3] but this incidence cannot be directly extrapolated to allogeneic HSCT recipients. For instance, autologous HSCT recipients are not at risk of GvHD and have a lower risk of hepatic veno-occlusive disease, both of which are associated with vascular disruption and prolonged systemic inflammation. Many autologous HSCT recipients are also increasingly exposed to thrombophilic medications such as lenalidomide for multiple myeloma (MM), which creates a VTE risk profile that is different from allogeneic HSCT recipients.

Limited studies in allogeneic HSCT recipients have reported a wide range in the incidence of VTE, from 0.5% to 13%.[4-10] The older studies are difficult to interpret as allogeneic transplant practices have changed over time. For example, a study that examined the risk of VTE in a cohort of over 400 HSCT recipients included patients receiving heparin as prophylaxis for veno-occlusive disease.[11] This is no longer a common strategy and would have altered the incidence of VTE. A recent meta-analysis of 12 studies in allogeneic HSCT recipients estimated the cumulative incidence of VTE at 4% (95% CI 2–6%), but was fraught with significant heterogeneity between studies (I2=80).[12]

Although some studies have described an association between GvHD and the risk of VTE, the follow up was generally short, and insufficient to determine if the risk of VTE changes over time.[10,13] The largest cohort study of 1514 HSCT recipients (including approximately 60% autologous transplants), reported that 4.6% of patients developed VTE.[10] This study, however, had only 6 months of follow up after HSCT, making it difficult to establish an association between chronic GvHD and VTE. Furthermore, it included mostly myeloablative conditioning regimens, making it difficult to assess VTE incidence after reduced-intensity conditioning regimens.

We therefore sought to rigorously examine the risk of VTE after first allogeneic HSCT in a large retrospective cohort of patients uniformly treated at a single center, describing VTE incidence, sites of involvement, risk associations and outcomes. The significant strength of this cohort at the Dana-Farber Cancer Institute/Brigham and Women's Hospital is that patients remain under the care of their transplant physicians long-term, creating a cohort with extended follow up of outcomes after HSCT.

In allogeneic HSCT it is also important to identify subgroups at the highest VTE risk that might benefit disproportionately from thromboprophylaxis, recognizing also the potential for harm associated with anticoagulation due to the higher risk of bleeding during thrombocytopenia and intestinal inflammation, as well as drug interactions with anticoagulants and GvHD medications. We therefore undertook further analyses in this cohort to determine if conventional VTE risk factors could identify a cohort of patients at particularly high risk for VTE after HSCT, who could potentially benefit from VTE prophylaxis.

Methods

Patients

We studied a retrospective cohort of 2276 patients who underwent first allogeneic HSCT between January 1, 2002 and December 31, 2013 at the Dana-Farber Cancer Institute/Brigham and Women's Hospital. Patient, transplant, and outcome related factors were extracted from both the transplantation database and through medical chart review. Outpatient pharmacy records and subsequent medical chart review identified patients with VTE on systemic anticoagulation. This study was approved by the Dana-Farber/Harvard Cancer Center institutional review board.

Definitions

Venous thromboembolism sites were categorized as lower extremity deep vein thrombosis or pulmonary embolism (LE DVT/PE), upper extremity and other. LE DVT/PE included PE, symptomatic proximal or distal lower extremity DVT, and the combination of PE and DVT, requiring systemic treatment. Upper extremity VTE included any arm DVT with or without a concurrent central line or peripherally inserted central catheter in place. Other VTE included superior vena cava (SVC), pelvic, abdominal, or right-sided ventricular thrombosis requiring systemic treatment. VTE was defined as an event confirmed by radiologic imaging (ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) or ventilation–perfusion (V/Q) scan) requiring systemic anticoagulation that occurred after stem cell infusion (ie., day 0 of HSCT). Systemic anticoagulation included low-molecular-weight heparin, warfarin, fondaparinux, and dabigatran. At our center, patients do not receive systemic thromboprophylaxis at the time of HSCT due to the expected fall in platelet count. If, however, patients are re-admitted with normal platelet counts and normal renal function, the standard of care at our center would include enoxaparin 40 mg subcutaneously daily or unfractionated heparin 5000 units subcutaneously three times a day for VTE prevention. For systemic therapy of VTE, practitioners at our center manage anticoagulation. If patients were on warfarin, they were managed by a central anticoagulation monitoring service. Information on the duration of anticoagulation and choice of anticoagulant was not obtained.

Statistical analysis

Patient baseline characteristics were reported descriptively. Endpoints of interest were overall survival, progression-free survival, relapse, and non-relapse mortality. Overall survival was defined as the time from stem cell infusion to death from any cause. Patients who were alive or lost to follow up were censored at the time last seen alive. Progression-free survival was defined as the time from stem cell infusion to disease relapse, progression or death from any cause, whichever occurred first. Patients who were alive without disease relapse or progression were censored at the time last seen alive and progression-free. A cumulative incidence curve of VTE was constructed in the competing risks framework considering death without developing VTE as a competing event. All time to events were measured from the date of stem cell infusion. The analysis is composed of two cohorts: the entire study population (N=2276) for identifying patient and transplant-related factors that are associated with post-HSCT VTE; and a subgroup of patients (N=168) to additionally investigate known VTE risk factors in depth. For the entire study population (N=2276), univariable and multivariable Cox regression analysis was performed to examine whether occurrence of VTE was a risk factor for overall survival, progression-free survival, relapse, non-relapse mortality, and chronic GvHD. Risk factors considered in multivariable analysis included age, patient and donor sex combination, disease risk index (DRI),[14] graft source, donor HLA type, comorbidity index,[15] sirolimus use as GvHD prophylaxis, body mass index (BMI), disease type (myeloid *vs.* other), acute and chronic GvHD, and

occurrence of VTE. Occurrence of VTE and acute and chronic GvHD were analyzed as time-dependent covariates. GvHD had to occur prior to the VTE event to be considered as a risk factor for VTE. Cox models were stratified by conditioning intensity because conditioning intensity did not meet the proportional hazards assumption. To identify potential risk factors for VTE, univariable and multivariable Cox regression analysis was utilized. For the subgroup analysis (N=168), we included all recent VTE events over a fixed time interval from January 1, 2010 to December 31, 2012 (N=56), with a control cohort of 112 HSCT patients who were randomly selected from 721 patients without VTE in the same transplantation period in a 1:2 ratio between cases and controls. To preserve the ability to test the association between risk factors and VTE, the control cohort was a random subset of patients without VTE and not matched on the characteristics of VTE cases. There were no significant differences in age, patient sex, donor sex, sex mismatch, BMI, diagnosis, DRI, donor type, conditioning intensity, cell source, or cytomegalovirus (CMV) seropositive status between the randomly selected and nonselected controls (all *P*-values >0.5). Using this subset of patients with and without VTE, we additionally collected baseline conventional risk factors known to be associated with VTE: a past medical history of diabetes, dyslipidemia, hypertension, prior myocardial infarction, prior stroke, and prior VTE. From pharmacy records, we also collected information on the use of hormone replacement therapy (HRT) in women from the time of HSCT onwards.

All analyses were done using SAS 9.3 (SAS Institute Inc., Cary, NC, USA), and R version 3.2.2 (The Comprehensive R Archive Network (CRAN) project). Multiplicity was not considered and the significance level was set to 0.05.

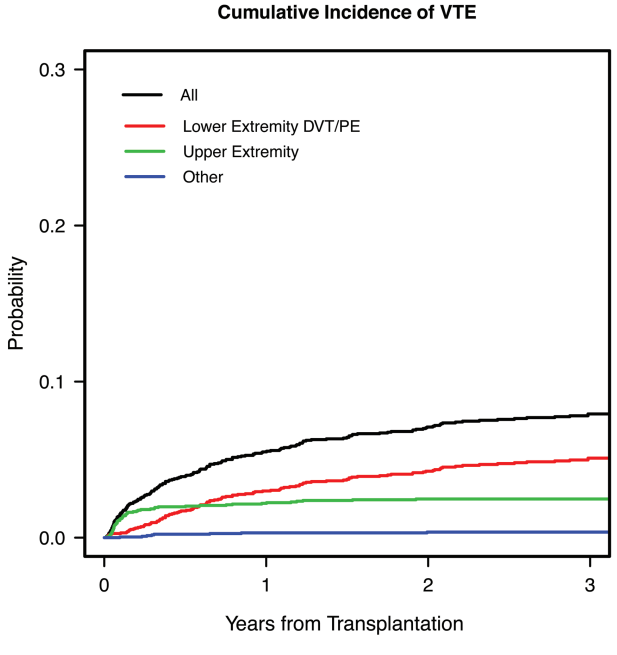

Figure 1. Cumulative Incidence of VTE after HSCT. The 1-year cumulative incidence of any VTE event after HSCT was 5.5% and the 2-year cumulative incidence was 7.1%, with LE DVT/PE being the most common type of VTE. DVT/PE: deep vein thrombosis or pulmonary embolism; VTE: venous thromboembolism.

Results

Incidence and Timing of VTE after HSCT

Between January 1, 2002 and December 31, 2013, 2276 patients underwent first-time allogeneic HSCT. The median follow-up time was 50 months (range 4-146) among survivors. Of these patients, 190 (8.3%) developed VTE requiring systemic anticoagulation. The 1- and 2-year cumulative incidence of all VTE were 5.5% (95% CI 4.6-6.5%) and 7.1% (95% CI 6.1-8.2%), respectively, Figure 1. Amongst the 190 patients who developed VTE, 120 (62.3%) were LE DVT/PE (45 were PE, 65 were lower extremity DVT and 10 were both PE and DVT), 57 (30%) were upper extremity (48 had a catheter *in situ* at time of thrombosis, 9 had a catheter removed less than one month prior to arm DVT) and 13 (6.8%) were other VTE (4 of which were SVC thrombosis). Upper extremity VTE occurred at a median of 1.3 months (range 0.1-41.1) after HSCT, which was significantly shorter than LE DVT/PE (9.2 months, range 0.2-72.3) and other VTE (10.2 months, range 1.1-67.1), *P*<0.0001 (Figure 2).

Platelet count at Time of VTE

Platelet count at time of VTE diagnosis in 176 patients was established by chart review. In 56 patients with an upper extremity VTE, the median platelet count at VTE diagnosis was 114.5 × 10^9/L (range 14-298), lower than for LE DVT/PE (N=108, median 142× 10^9/L, range 22-474) and other VTE (N=12, median 192.5 × 10^9/L, range 42-473), *P*=0.0046. The median platelet count at time of any VTE event was 130.5 × 10^9/L (range 14-474).

Risk Factors for VTE

Evaluating usual patient, disease and transplant variables, there was no difference in age, sex, BMI, diagnosis, DRI, conditioning regimen intensity, donor type (HLA-matched or HLA-mismatched, related or unrelated, or cord blood), or graft source (bone marrow or peripheral blood) between allogeneic HSCT recipients with and without VTE (Table 1).

In a multivariable model to identify potential risk factors for VTE, both acute and chronic GvHD were independently associated with developing any type of VTE (HR=2.05, 95% CI 1.52-2.76, *P*<0.0001 and HR=1.71, 95% CI 1.19-2.46, *P*=0.0035, respectively), Table 2. As median time of VTE after HSCT and platelet count at time of VTE were significantly different for upper extremity VTE *versus* other types of VTE, we further performed multivariate models separating these types of VTE events. When examining upper extremity VTE only, conditioning regimen intensity, donor type and acute and chronic GvHD were risk factors for VTE. When upper extremity VTE was excluded, donor type (matched unrelated donor (MUD) *vs.* matched related donor (MRD), mismatched vs. MRD), myeloid disease and both acute and chronic GvHD were associated with all other VTE (Table 2).

In patients who had a VTE after HSCT, 98 patients (51.6%) had active GvHD on therapy, 28 patients (14.7%) no longer had active GvHD but remained on therapy, 54 patients (28.4%) were on a GvHD prophylaxis regimen and 10 patients (5.3%) had no history of GvHD and were not on immunosuppressive therapy. The most common immunosuppressive regimens for patients with a VTE were tacrolimus and prednisone (N=35, 19.3%), tacrolimus and sirolimus (N=32, 17.7%) and tacrolimus,

sirolimus and prednisone (N=26, 14.4%). In patients who developed GvHD after their first VTE, 8% had a subsequent VTE event. For patients with active or previous GvHD at the time of VTE, the most prevalent organ involved was the skin, including sclerodermatous GvHD (N=83, 65.9%), followed by gastrointestinal GvHD (N=37, 29.4%), ocular and/or oral GvHD (N=36, 28.6%) and liver GvHD (N=27, 21.4%).

In order to compare conventional VTE risk factors, we performed a subset case control analysis between HSCT recipients with and without VTE. The only conventional risk factor associated with a risk of VTE after HSCT was a prior history of VTE before HSCT. The incidence of prior VTE was higher in patients who developed VTE after HSCT: only 10 out of 112 patients (8.9%) without VTE after HSCT had a prior VTE event, while 12 out of 56 patients (21.4%) with VTE after HSCT had a prior VTE event (P=0.03, Table 3).

Clinical Outcomes

In multivariable analysis, any VTE event was associated with increased non-relapse mortality (HR=1.47; 95% CI 1.08-2.00; P=0.015), but not with relapse (HR=0.88, 95% CI 0.63-1.23; P=0.47), progression-free survival (HR=1.13, 95% CI 0.90-1.41; P=0.29) or overall survival (HR=1.05, 95% CI 0.84-1.31; P=0.65). Evaluating by site of VTE, upper extremity VTE alone did not impact any clinical outcome including non-relapse mortality. LE DVT/PE and other VTE remained significantly associated with non-relapse mortality (HR=1.71; 95% CI 1.17-2.49; P=0.005). Table 4 summarizes the multivariable models.

Discussion

Venous thromboembolism in cancer is well described, but the incidence and risk factors after allogeneic HSCT, a presumptively curative therapy for aggressive hematologic malignancies, is not well defined. While treating the underlying malignancy with allogeneic HSCT can reduce the risk of VTE, the study herein reports that the incidence of VTE post-HSCT remains high. In the largest allogeneic HSCT cohort evaluated to date with a median follow up of over 4 years, we demonstrated a very high incidence of VTE of 8.3%. We found that acute and chronic GvHD were independent risk factors for developing VTE. A prior history of VTE was also significantly associated with developing VTE in this cohort of patients. Lower extremity DVT and PE, as well as VTE in unusual locations such as splanchnic veins, was associated with an increased risk

Table 1. Baseline Characteristics of Patients with and without VTE after HSCT.

N (%)	No VTE (N=2086)	VTE (N=190)	P
Age, median (range)	52 (17, 74)	53 (20, 73)	0.1
Male	1220 (58.5%)	111 (58.4%)	1
Body mass index >= 30	582 (27.9%)	59 (31.1%)	0.36
Male patient with Female donor	475 (22.8%)	41 (21.6%)	0.79
Diagnosis			
Acute leukemia	937 (44.9%)	71 (37.4%)	0.1
Lymphoma	411 (19.7%)	44 (23.1%)	
Multiple myeloma	59 (2.8%)	3 (1.6%)	
Other	679 (32.6%)	66 (34.7%)	
Donor Type			
Matched unrelated	1031 (49.4%)	100 (52.6%)	0.71
Matched related	746 (35.8%)	66 (34.7%)	
Mismatched unrelated	283 (13.6%)	21 (11.1%)	
Mismatched related	26 (1.2%)	3 (1.6%)	
Disease Risk Index			
Low	381 (18.7%)	36 (19.4%)	0.57
Intermediate	1030 (50.7%)	102 (54.8%)	
High	545 (26.8%)	43 (23.1%)	
Very high	77 (3.8%)	5 (2.7%)	
Conditioning Intensity			
Myeloablative	875 (41.9%)	83 (43.7%)	0.65
Reduced intensity	1211 (58.1%)	107 (56.3%)	
Graft Source			
Bone marrow	161 (7.7%)	11 (5.8%)	0.17
Peripheral blood	1785 (85.6%)	174 (91.6%)	
Umbilical cord	136 (6.5%)	5 (2.6%)	
Type of VTE			
Lower extremity DVT/PE	---	120 (62.3%)	---
Upper Extremity VTE		57 (30%)	
Other VTE		13 (6.8%)	

HSCT: hematopoietic stem cell transplantation; VTE: venous thromboembolism: DVT/PE: deep vein thrombosis or pulmonary embolism.

of non-relapse mortality (HR=1.71). Although allogeneic HSCT recipients have a 2.5% incidence of upper extremity VTE (which is associated with central venous catheters), thrombosis at this site was not associated with increased non-relapse mortality. Upper extremity VTE represents a unique cohort of patients with VTE, as evidenced by the shorter time to VTE after HSCT which reflects that these events were due to central venous catheter placement routinely used during conditioning chemotherapy and HSCT at our center. The lower platelet count observed with upper extremity VTE also likely reflects the early timeframe when VTE was diagnosed in this cohort, reflecting that these patients were still undergoing platelet recovery after HSCT.

Prior to this study, the largest cohort examining VTE in HSCT recipients by Gerber and colleagues reported that

Table 2. Multivariable Model of HSCT Variables Associated with VTE.

Outcome	Variable	HR (95% CI)	*P**
All VTE	Acute GvHD	2.05 (1.52-2.76)	<.0001*
	Chronic GvHD	1.71 (1.19-2.46)	0.0035*
LE DVT/PE and Other VTE	MUD (6/6) *vs.* MRD	1.66 (1.12-2.47)	0.012*
	Mismatched *vs.* MRD	1.86 (0.98-3.52)	0.057
	Myeloid *vs.* non- myeloid	0.66 (0.47-0.93)	0.019*
	Acute GvHD	1.89 (1.32-2.71)	0.0005*
	Chronic GvHD	1.94 (1.23-3.05)	0.0044*
Upper Extremity VTE	RIC *vs* MAC	0.46 (0.26-0.81)	0.0075*
	MUD (6/6) *vs.* MRD	0.48 (0.27-0.84)	0.0109*
	Acute GvHD	2.13 (1.14-3.97)	0.0173*
	Chronic GvHD	3.39 (1.17-9.85)	0.025*

*Indicates statistical significance. MUD: matched unrelated donor; MRD: matched related donor. RIC: reduced intensity conditioning; MAC: myeloablative conditioning; HSCT: hematopoietic stem cell transplantation; HR: hazard ratio; CI: confidence interval; VTE: venous thromboembolism; LE DVT/PE: lower extremity deep vein thrombosis or pulmonary embolism; GvHD: graft-*versus*-host disease

Table 3. Subgroup analysis of Conventional VTE Risk Factors in HSCT Recipients.

N (%)	No VTE (N=112)	VTE (N=56)	*P**
Diabetes	7 (6.3%)	5 (8.9%)	0.54
Dyslipidemia	29 (25.9%)	9 (16.1%)	0.17
Hypertension	27 (24.1%)	13 (23.2%)	1
Prior myocardial infarction	5 (4.5%)	2 (3.6%)	1
Prior VTE	10 (8.9%)	12 (21.4%)	0.03*
Prior stroke	0	0	N/A
Smoking status			
Current smoker	12 (10.7%)	2 (3.6%)	0.23
Ex-smoker	37 (33%)	17 (30.4%)	
Non-smoker	63 (56.3%)	37 (66.1%)	
HRT (women only)	13 (25%)	6 (37.5%)	0.35

*Indicates statistical significance. HRT: hormone replacement therapy; HSCT: hematopoietic stem cell transplantation; VTE: venous thromboembolism.

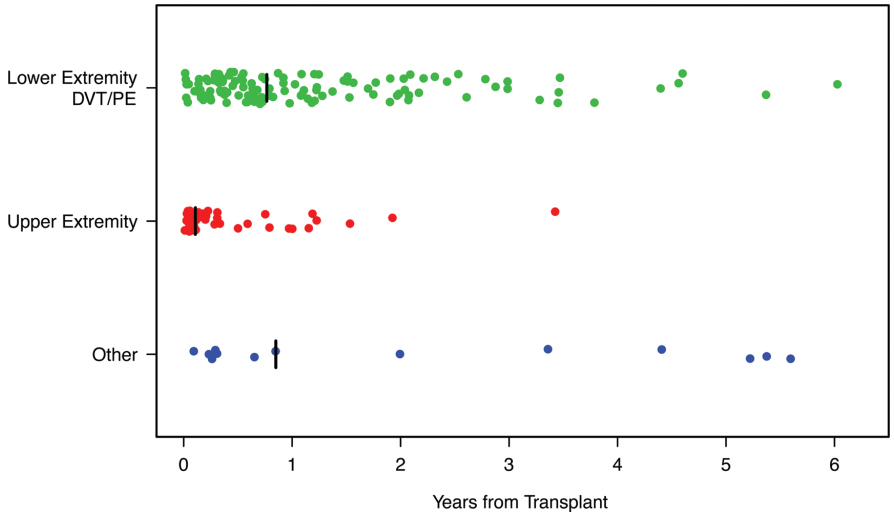

Figure 2. Timing of VTE after HSCT. Each dot represents one VTE event after HSCT. Upper extremity VTE occurred at a median of 1.3 months after HSCT, whereas LE DVT/PE occurred at a median of 9.2 months and other VTE at a median of 10.2 months (upper extremity *versus* LE DVT/PE and other, *P*<0.0001). DVT/PE: deep vein thrombosis or pulmonary embolism.

Table 4. Multivariable Analysis of VTE and HSCT Clinical Outcomes.

HR (95% CI)	Overall Survival	Progression-free Survival	Non-relapse Mortality	Relapse
All VTE	1.05 (0.84-1.31)	1.13 (0.90-1.41)	1.47 (1.08-2.00)*	0.88 (0.63-1.23)
LE DVT/PE and Other VTE	1.18 (0.90-1.55)	1.24 (0.93-1.65)	1.71 (1.17-2.49)*	0.87 (0.56-1.36)
Upper Extremity	0.86 (0.59-1.25)	0.98 (0.69-1.39)	1.15 (0.69-1.90)	0.89 (0.54-1.46)

*Indicates statistical significance. HR: hazard ratio; CI: confidence interval; HSCT: hematopoietic stem cell transplantation; VTE: venous thromboembolism; LE DVT/PE: lower extremity deep vein thrombosis or pulmonary embolism.

4.6% of patients developed VTE,[10] but that study differs significantly from our analysis as it includes patients treated with autologous transplant who were excluded from our cohort. Gerber's study also included mainly myeloablative conditioning, which differs from our report in which about 60% of patients received reduced intensity conditioning. One could hypothesize that myeloablative conditioning may increase the incidence of VTE due to more vascular endothelial damage, veno-occlusive disease (VOD), and organ toxicity, but this was not the case in our multivariate models for VTE risk. Conditioning intensity was only associated with upper extremity VTE, perhaps because patients receiving myeloablative conditioning are more likely to have an indwelling central line for a longer time.

In the study herein, GvHD was independently associated with VTE after HSCT. We postulate that GvHD does indeed induce a pro-inflammatory state which likely makes patients more prone to VTE. As this was a database study, we were limited by the data collected and did not have enough information regarding GvHD therapy or immobilization. Of note, we did see a high incidence of skin GvHD (65%) in patients who developed VTE which could be due to a decreased mobility of limbs and possible impact on venous return. This is merely hypothesis generating at this point and as such requires a prospective analysis of VTE after HSCT.

The limitations of our study are related to the constraints of database research and our reliance on outpatient pharmacy records to identify patients on anticoagulation who were then assessed for VTE. The incidence of VTE captured may therefore be an underestimation of the true rate of VTE. Patients who had an inpatient thrombotic episode but were not treated as an outpatient would have been missed, although this number is likely to be small, as most patients receive a minimum of 3 months of anticoagulation which is generally longer than hospital admissions for HSCT recipients. Patients who had contraindications to anticoagulation, such as thrombocytopenia, would also have been missed. While our overall incidence of VTE at 8.3% is high, this may be an underestimation given the aforementioned limitations in identifying all cases, reinforcing the message that VTE is a prevalent and concerning complication after allogeneic HSCT. Variables that could not be formally addressed in this analysis included incidence of VOD and cause of death.

In an effort to assess for VTE risk factors, we evaluated both standard HSCT and VTE related variables, and also evaluated sirolimus use in the multivariate analysis. Patients receive sirolimus either as GvHD prophylaxis or treatment. There is literature suggesting that the use of sirolimus is associated with vascular disruption, possibly leading to more vascular complications such as VTE.[16-18] In our analysis, we did not find an association between sirolimus and VTE incidence, suggesting that GvHD itself, and not treatment with sirolimus, is the risk factor for developing VTE. We do however recognize that the number of patients in each of the GvHD prophylaxis/therapeutic categories is small, and thus this analysis is likely not sufficiently powered to draw any firm conclusions regarding the impact of immunosuppressive medications on the risk of VTE in HSCT.

Although we documented an increased risk of VTE after HSCT, it is difficult to make recommendations about routine thromboprophylaxis without further study. Current CHEST guidelines recommend thromboprophylaxis for hospitalized patients with a VTE risk greater than 10%,[19] while the International Society on Thrombosis and Haemostasis (ISTH) guidelines recommend that patients with a Khorana risk score of 3 or more and a VTE risk of about 7%, receive thromboprophylaxis,[20] as the high rates of VTE justify the risk of bleeding from anticoagulation in these patient groups. In our population, the cumulative 1-year and 2-year incidence of VTE in all allogeneic HSCT patients was 5.5% and 7.1%, respectively, which would be within the range of the current recommendations. For patients with normal platelet counts, no additional bleeding risk, active GvHD and prior history of VTE, thromboprophylaxis could be considered. Carefully designed prospective interventional trials of thromboprophylaxis after allogeneic HSCT are needed, targeting the subsets of patients that we have identified as being at the highest risk of VTE.

References

1. Barlogie B, Tricot G, Anaissie E, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. N Engl J Med. 2006;354(10):1021-1030.
2. Lonial S, Kaufman J, Tighiouart M, et al. A phase I/II trial combining high-dose melphalan and autologous transplant with bortezomib for multiple myeloma: a dose- and schedule-finding study. Clin Cancer Res. 2010;16(20):5079-5086.
3. Krishnan A, Pasquini MC, Logan B, et al. Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. Lancet Oncol. 2011;12(13):1195-1203.
4. de Lima M, Anagnostopoulos A, Munsell M, et al. Nonablative versus reduced-intensity conditioning regimens in the treatment of acute myeloid leukemia and high-risk myelodysplastic syndrome: dose is relevant for long-term disease control after allogeneic hematopoietic stem cell transplantation. Blood. 2004;104(3):865-872.
5. Russell JA, Duan Q, Chaudhry MA, et al. Transplantation from matched siblings using

once-daily intravenous busulfan/fludarabine with thymoglobulin: a myeloablative regimen with low nonrelapse mortality in all but older patients with high-risk disease. Biol Blood Marrow Transplant. 2008; 14(8):888-895.
6. Maris MB, Sandmaier BM, Storer BE, et al. Unrelated donor granulocyte colony-stimulating factor-mobilized peripheral blood mononuclear cell transplantation after nonmyeloablative conditioning: the effect of postgrafting mycophenolate mofetil dosing. Biol Blood Marrow Transplant. 2006;12(4): 454-465.
7. 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(9):1468-1473.
8. Azik F, Gokcebay DG, Tavil B, Isik P, Tunc B, Uckan D. Venous thromboembolism after allogeneic pediatric hematopoietic stem cell transplantation: A single-center study. Turk J. Haematol. 2015;32(3):228-233.
9. Labrador J, Gonzalez-Rivero J, Monroy R, et al. Management patterns and outcomes in symptomatic venous thromboembolism following allogeneic hematopoietic stem cell transplantation. A 15-years experience at a single center. Thromb Res. 2016; 142:52-56.
10. Gerber DE, Segal JB, Levy MY, Kane J, Jones RJ, Streiff MB. The incidence of and risk factors for venous thromboembolism (VTE) and bleeding among 1514 patients undergoing hematopoietic stem cell transplantation: implications for VTE prevention. Blood. 2008;112(3):504-510.
11. Pihusch R, Salat C, Schmidt E, et al. Hemostatic complications in bone marrow transplantation: a retrospective analysis of 447 patients. Transplantation. 2002;74(9): 1303-1309.
12. 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(9):1457-1464.
13. Labrador J, Lopez-Anglada L, Perez-Lopez E, et al. Analysis of incidence, risk factors and clinical outcome of thromboembolic and bleeding events in 431 allogeneic hematopoietic stem cell transplantation recipients. Haematologica. 2013;98(3):437-443.
14. Armand P, Kim HT, Logan BR, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. Blood. 2014;123(23):3664-3371.
15. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005;106(8):2912-2919.
16. Guba M, Yezhelyev M, Eichhorn ME, et al. Rapamycin induces tumor-specific thrombosis via tissue factor in the presence of VEGF. Blood. 2005;105(11):4463-4469.
17. Schuetze SM, Zhao L, Chugh R, et al. Results of a phase II study of sirolimus and cyclophosphamide in patients with advanced sarcoma. Eur J Cancer. 2012; 48(9):1347-1353.
18. Xu L, Qin Y, Huang J, et al. Effect of rapamycin-induced tumor vessel thrombosis combined with docetaxel in non-small-cell lung cancer. Anticancer Drugs 2013; 24(4):406-414.
19. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). Chest J. 2008;133(6 Suppl):381S-453S.
20. Khorana AA, Otten HM, Zwicker JI, Connolly GC, Bancel DF, Pabinger I. Prevention of venous thromboembolism in cancer outpatients: guidance from the SSC of the ISTH. J Thromb Haemost. 2014; 12(11):1928-1931.