Incidence of symptomatic venous thromboembolism following hematopoietic stem cell transplantation

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Summary. Background: The incidence of symptomatic venous thromboembolism (VTE) following hematopoietic stem cell transplantation (HSCT) is not well described, particularly with increased use of ambulatory care in the transplant setting. Methods: A retrospective analysis involving 589 patients (382 autologous HSCT, 207 allogeneic HSCT) undergoing transplantation between 2000 and 2005 in a single Canadian institution was undertaken to identify the incidence of proximal deep vein thrombosis (DVT) or pulmonary embolism (PE) in HSCT patients. Results: The total 1-year incidence of symptomatic VTE was 3.7% [95% confidence interval (CI) 2.5–5.6]. Among the HSCT patients, 7/589 (1.2%, 95% CI 0.6–2.4) developed symptomatic non-catheter-related VTE following HSCT (four PE and three DVT). All VTE events occurred after hematopoietic engraftment. Patients undergoing autologous HSCT did not receive thromboprophylaxis, whereas most patients undergoing allogeneic HSCT (79.7%) received enoxaparin 20 mg daily for the prevention of veno-occlusive disease of the liver, starting 6 ± 3 days before transplantation for a mean of 22 ± 14 days. Conclusion: HSCT patients have a high incidence of VTE. Thromboprophylaxis should potentially be considered in these patients. However, future studies assessing the risk and benefits of thromboprophylaxis are needed in this specific population.

Keywords: ambulatory care, hematopoietic transplantation, incidence, pulmonary embolism, thrombosis.

Introduction

The incidence of venous thromboembolic events after hematopoietic stem cell transplantation (HSCT) is not well defined. Patients undergoing HSCT have several risk factors for developing venous thromboembolism (VTE). These include underlying malignancy, high-dose myeloablative chemotherapy treatment and/or total body radiation, prolonged hospital admissions leading to periods of immobility, and the universal presence of indwelling central venous catheters. Prior studies have also demonstrated that patients undergoing HSCT have increased thrombin generation, decreased fibrinolysis, decreased antithrombin III levels, and endothelial cell damage [1–10]. Furthermore, a recent study has shown that children undergoing allogeneic HSCT develop a state of acquired thrombophilia (decreased protein C and antithrombin levels) in the early HSCT period [11]. Importantly, patients undergoing HSCT rarely receive thromboprophylaxis, due to the risk of bleeding related to thrombocytopenia.

There is an emerging trend towards increased ambulatory care in HSCT centers, in contrast to more traditional programs, where patients remain in hospital throughout the acute post-transplant period. Determining the incidence of VTE following autologous and allogeneic HSCT in the era of increased ambulatory care would improve our understanding of the risks and benefits associated with this model of care. Furthermore, decisions regarding thromboprophylaxis could be considered with current information in this population. Therefore, we investigated the incidence of VTE in a cohort of patients who underwent autologous and allogeneic HSCT in an ambulatory HSCT program.

Patients and methods

Patients

All patients undergoing autologous or allogeneic HSCT between 2000 and 2005 at a Canadian tertiary care center were included in the study. Patients were excluded if they did not provide signed consent for the use of medical information for research purposes. The protocol was approved by the institutional research ethics board. Patient data were extracted from the Blood and Marrow Transplantation (BMT) database at our institution. Information regarding specific cases was obtained from the hospital records.
The BMT program at our institution has routinely performed HSCT procedures since 1992 in an ambulatory setting that allows patients to remain outpatients during a significant portion of the transplant period [12]. Rather than being restricted continuously to a hospital environment during their pre-transplant conditioning treatment and the immediate post-transplant phase, patients are seen and assessed on a daily basis in the day hospital. Patients are transferred to the ward for continuous inpatient care if they develop complications, can no longer move to and from the hospital, live far away from the hospital, or lack an appropriate care-giver.

Patients undergoing allogeneic HSCT during the time period under study were routinely given enoxaparin 20 mg daily by subcutaneous injection for the prevention of veno-occlusive disease. The low molecular weight heparin dose was withheld if the patient was bleeding or if they developed refractory thrombocytopenia. In addition, enoxaparin was stopped if patients were receiving active treatment with other anticoagulants for treatment of VTE. In general, enoxaparin was stopped when patients were discharged from the transplant unit.

Identifying cases of VTE

The primary endpoint of the study was acute symptomatic VTE. VTE included pulmonary embolism (PE) or non-catheter-related deep vein thrombosis (DVT). Secondary endpoints included upper extremity catheter-related thrombosis and the number of days following transplantation until the development of VTE. Catheter-related thrombosis was defined as mural thrombus with partial or total occlusion of a vessel in which a catheter was present or had been present within the prior 30 days, confirmed by compression or color ultrasound.

All reports of imaging studies performed within 1 year following HSCT were reviewed for each patient and screened for any description of thrombosis or embolism. In addition, all reports of chest computed tomography (CT) scans with intravenous contrast, ventilation/perfusion (V/Q) scans and Doppler ultrasound scans of upper and lower extremities were reviewed. Reports were then reviewed independently by two experts (DA, MC) to identify cases of extremity DVT, PE or catheter-related thrombosis. VTE was defined by one of three criteria: (i) a high-probability V/Q scan combined with a high or moderate clinical pretest probability according to the Wells' model (score $> 2$) [13]; (ii) a spiral CT scan of the chest demonstrating an intraluminal filling defect in a segmental pulmonary artery or larger vessel combined with a high or intermediate clinical pretest probability; or (iii) a proximal DVT on venous compression ultrasonography in a symptomatic extremity. In cases where DVT and PE occurred together, the events were classified as PE.

In all cases of VTE, the disease status at the time of VTE diagnosis was confirmed using the information obtained from the hospital medical record. In cases of VTE occurring after allogeneic HSCT, the occurrence of acute and chronic graft vs. host disease (GVHD) was obtained from the BMT database, and details were obtained from the hospital medical record. Information regarding the treatment for all cases of VTE was extracted from the medical records.

Central venous catheters

Central venous catheters were placed in an upper extremity prior to transplant in all patients. Catheters remained in place until hematopoietic recovery in all patients unless the catheter was suspected or proven to be infected. Catheters were removed in autologous HSCT patients once they were no longer transfusion-dependent. Catheters were maintained in allogeneic HSCT patients at risk for cytomegalovirus (CMV) reactivation (positive recipient or donor CMV serology prior to transplantation) until approximately day 100. In all other allogeneic HSCT patients, catheters were typically removed following hematopoietic engraftment. Central catheters were flushed once weekly, and the dressing was changed once weekly or as needed.

In cases of DVT of the upper extremity, management included removal of the catheter and/or anticoagulation using low molecular weight heparin.

Statistical methods

Student’s $t$-test was used to compare mean values using a two-tailed analysis, and chi-squared or exact Fisher test analysis was used to compare proportions using GraphPad.

Results

Incidence of VTE

Characteristics of the patients reviewed in this study are shown in Table 1. After evaluation of 382 autologous and 207 allogeneic HSCT patients, 22 [3.7%, 95% confidence interval (CI) 2.5–5.6] cases of symptomatic VTE were identified within 1 year of HSCT. Ten patients (4.8%, 95% CI 2.6–8.7) had VTE after autologous HSCT, whereas 12 patients (3.1%, 95% CI 1.8–5.4; $P = 0.30$) had VTE after autologous HSCT. A summary of results is provided in Table 2.

If we consider non-catheter-related events separately, seven (1.2%, 95% CI 0.6–2.4) symptomatic VTEs were identified within the first year following HSCT. Five patients (2.4%, 95% CI 1.0–5.5) were diagnosed with VTE (one DVT, four PE) in the allogeneic HSCT group, as compared with only two (both proximal lower extremity DVT) in the autologous HSCT group (0.5%, 95% CI 0.1–1.9%, $P = 0.06$). PE was more frequent in the allogeneic HSCT group than in the autologous HSCT group (4 vs. 0, $P = 0.01$).

Symptomatic catheter-related VTE was diagnosed in five (2.4%, 95% CI 1.0–5.5) allogeneic HSCT patients and in 10 (2.6%, 95% CI 1.4–4.8) autologous HSCT patients ($P = 0.88$). All of the upper extremity events occurred in the presence of a central venous catheter.
Patients undergoing autologous HSCT did not receive thromboprophylaxis, whereas most patients undergoing allogeneic HSCT (79.7%) received enoxaparin 20 mg daily for the prevention of veno-occlusive disease of the liver, starting 6 ± 3 days before transplantation for a mean of 22 ± 14 days (median 26, range 1–60 days).

Timing of VTE after HSCT

The mean time to VTE following HSCT was 153 days (range 71–219) in the allogeneic HSCT group and 312 days (range 256–368) in the autologous HSCT group ($P = 0.080$). Interestingly, no patient developed VTE during the initial hospitalization following HSCT or prior to hematopoietic engraftment. One patient developed VTE during a subsequent hospital admission for septicemia at day 71. All other patients were treated and diagnosed as outpatients (Table 3).

Disease status at time of VTE and role of GVHD

Table 3 summarizes the characteristics of patients with symptomatic VTE. In the allogeneic HSCT group, four of five patients were in complete remission at the time of VTE diagnosis, and one patient developed PE in the setting of relapsed acute myelogenous leukemia 71 days after HSCT. In the autologous HSCT group, both patients had relapsing disease present at the time of VTE. One patient had relapsed transformed indolent lymphoma occurring 1 year post-HSCT, and the second patient had a recurrence of immunoblastic lymphoma diagnosed 8 months post-HSCT at the time of VTE.

In the allogeneic HSCT group, three non-catheter-related VTEs occurred in a subgroup of 75 patients (4.0%) who developed acute GVHD of any grade following HSCT. One patient developed acute GVHD and was subsequently diagnosed with VTE by day 110. The cumulative incidence of acute GVHD before day +100 (grades I–IV) in our cohort of allogeneic HSCT patients was 36%. Of the remaining 132 allogeneic HSCT patients who did not develop acute GVHD, no episodes of VTE occurred before day 100 (0%, $P = 0.02$); however, two episodes of VTE were identified later on days 219 and 274, and both of these patients were on immunosuppressive treatment for chronic GVHD diagnosed after day 100. The cumulative incidence of chronic GVHD was not available for the outpatient population.

None of the patients or donors had known thrombophilic disorders that were recorded in the medical record. Two patients had previous VTE events. There was no previous history of VTE in first-degree relatives in any of the patients with VTE after transplantation in our study. Catheter-related events are discussed below.

Table 3 Characteristics of autologous and allogeneic hematopoietic stem cell transplantation (HSCT) patients with a confirmed venous thromboembolism (VTE)

<table>
<thead>
<tr>
<th>Case</th>
<th>Event</th>
<th>Imaging</th>
<th>Transplant</th>
<th>Days post-HSCT</th>
<th>Hospital status</th>
<th>Disease status</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PE</td>
<td>V/Q</td>
<td>Allo</td>
<td>219</td>
<td>Inpatient</td>
<td>CR</td>
<td>LMWH</td>
</tr>
<tr>
<td>2</td>
<td>PE</td>
<td>CT</td>
<td>Allo</td>
<td>90</td>
<td>Outpatient</td>
<td>CR</td>
<td>LMWH and warfarin</td>
</tr>
<tr>
<td>3</td>
<td>PE</td>
<td>CT</td>
<td>Allo</td>
<td>110</td>
<td>Outpatient</td>
<td>CR</td>
<td>LMWH</td>
</tr>
<tr>
<td>4</td>
<td>PE</td>
<td>V/Q</td>
<td>Allo</td>
<td>71</td>
<td>Outpatient</td>
<td>Relapsed</td>
<td>LMWH</td>
</tr>
<tr>
<td>5</td>
<td>DVT</td>
<td>US</td>
<td>Allo</td>
<td>274</td>
<td>Outpatient</td>
<td>CR</td>
<td>LMWH</td>
</tr>
<tr>
<td>6</td>
<td>DVT</td>
<td>US</td>
<td>Auto</td>
<td>368</td>
<td>Outpatient</td>
<td>Relapsed</td>
<td>LMWH and warfarin</td>
</tr>
<tr>
<td>7</td>
<td>DVT</td>
<td>US</td>
<td>Auto</td>
<td>256</td>
<td>Outpatient</td>
<td>Relapsed</td>
<td>LMWH</td>
</tr>
</tbody>
</table>

PE, pulmonary embolism; DVT, deep vein thrombosis; CT, computed tomography; V/Q, ventilation/perfusion scan; US, Doppler ultrasound; Allo, allogeneic; Auto, autologous; CR, complete remission; LMWH, low molecular weight heparin.

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Treatment of VTE after bone marrow transplantation

At the time of VTE diagnosis, the mean platelet count was 121 (range 50–174). Three patients had platelet counts below normal, and all had VTE diagnosed in the context of relapsing disease. The four remaining patients had normal platelet counts at the time when VTE was diagnosed. All seven patients were treated with full-dose anticoagulation using low molecular weight heparin, but in two cases, low molecular weight heparin therapy was switched to treatment with warfarin. No significant bleeding complications developed during anticoagulant therapy in these seven patients.

Other transplant complications

Non-relapse mortality at day 100 after autologous HSCT occurred in 16 patients (4.2%) with no additional toxic fatalities within the first year after transplantation. Organ toxicity following HSCT was assessed using the Seattle criteria [14]. Severe mucositis of at least grade 2 occurred in 24% of patients, and gastrointestinal, renal, pulmonary and cardiac toxicity of at least grade 2 occurred in 13.3%, 9.1%, 8.4% and 7.8%, respectively. Hepatic, neurologic and bladder toxicity of grade 2 or more occurred less frequently (5.8%, 5.5% and 0.8%, respectively). Transplant-related toxicity was more common after allogeneic HSCT. Non-relapse mortality was 16% (33 patients) at day 100 and 24% at 1 year (51 patients). The most common organ toxicities of at least grade 2 were mucositis (48%), hepatic toxicity (29%), renal toxicity (26%), pulmonary compromise (20%), and gastrointestinal toxicity. Less common organ systems with serious toxicity of grade 2 or more after allogeneic HSCT were bladder (13%), cardiac (11%), and neurologic (11%).

Discussion

To our knowledge, this is the largest and most comprehensive examination of the incidence of symptomatic VTE in patients undergoing HSCT in a center with an established ambulatory care/outpatient model. Our study provides insights regarding the incidence of VTE as an important transplant-related complication in both allogeneic and autologous HSCT. HSCT patients have a high risk of symptomatic VTE. The rate of symptomatic VTE in the present analysis is comparable to the overall rate of symptomatic VTE reported in the randomized controlled trials assessing thromboprophyaxis in medically ill hospitalized patients using dalteparin (0.77%) and enoxaparin (1.04%) [15,16]. On the basis of these two studies, the American College of Chest Physician and the American Society of Clinical Oncology recommend considering the use of thromboprophyaxis in hospitalized medically ill and cancer patients respectively [17,18]. Although HSCT patients might benefit from thromboprophyaxis, the risks of bleeding may be increased due to the prolonged thrombocytopenia resulting from myeloablative therapy. Many patients undergoing allogeneic HSCT in our series received low-dose enoxaparin as prophylaxis against veno-occlusive disease of the liver, which may have offered some protection against the development of VTE. Convincing evidence for the use of low molecular weight heparin to prevent veno-occlusive disease of the liver is lacking [19]. Furthermore, the dose of enoxaparin used in our patients was studied in comparison with placebo in medically ill patients, and demonstrated no benefit in the prevention of VTE [15]. Moreover, the use of anticoagulants has been recently associated with increased risk of bleeding in patients undergoing HSCT [20]. Further research is required to assess the risks and benefits of thromboprophyaxis in this specific population.

Two previous retrospective cohort studies have reported a 1.3–4.9% overall incidence of non-catheter-related extremity DVT or PE in HSCT patients [20,21]. In these studies, VTE occurred more frequently following allogeneic HSCT [21] or in patients with prior VTE or concomitant GVHD [20]. In both studies, patients remained in hospital throughout the transplant period until the resolution of all acute issues. Although elevated, our rates are similar or lower than those previously published for HSCT patients. This may suggest that an ambulatory care model in blood and marrow transplantation [12] may potentially decrease the overall incidence of VTE following HSCT. It has been well demonstrated that hospitalization is an important risk factor for VTE in cancer patients [22], and the rate of VTE in hospitalized cancer patients is increasing over time [23]. It is possible that the emerging trend of ambulatory care for HSCT patients maintains greater patient mobility and contributes to a reduced risk of VTE following HSCT that extends beyond the acute period of hematopoietic engraftment. Prospective studies are required to confirm these findings.

The overall incidences of catheter-related VTE in our study are similar to those previously reported in HSCT patients [21] and in patients with hematologic malignancies [24]. The incidence of catheter-related VTE occurring early after HSCT was not different between allogeneic and autologous HSCT patients in our study. Recent meta-analyses of randomized trials of prophylaxis in cancer patients with central catheters suggest that warfarin and low molecular weight heparin are not beneficial [25–27]. Similar findings were reported for patients with hematologic malignancies, although these studies did not include HSCT patients [24]. Further research is required before recommendations on thromboprophyaxis to reduce catheter-related thrombosis can be made in patients undergoing HSCT.

All VTE events occurring after transplantation in our study developed beyond the acute period of hematopoietic engraftment. The higher incidence of VTE, and of PE in particular, in the allogeneic setting is consistent with a previously published report [21]. In this previous study, increased rates of VTE were observed in allogeneic transplant patients who developed chronic GVHD. A subsequent study by the same group confirmed an increased rate of VTE in patients with chronic GVHD [28]. In their study, four VTEs (including two cases of catheter-related thrombosis) were reported in 31 patients (12.9%) with chronic GVHD, as compared with only one event in 58 patients without chronic GVHD (1.7%, P < 0.05) [28].
Our cases support the possibility that acute GVHD is potentially an important contributing factor. Although acute GVHD is defined as GVHD occurring before day 100 after transplantation, chronic GVHD can occur for a period of several years following allogeneic transplantation and is a complex disease with recently developed diagnostic criteria and response criteria [29,30]. The limited follow-up of 1 year for patients included in our study precludes a more definitive analysis of VTE occurring in the context of chronic GVHD. Vascular and endothelial injury that occurs as a consequence of GVHD [31] may contribute to inflammation that increases the risk of venous thrombosis in allogeneic transplant recipients. Furthermore, the role of immunosuppressive medications used in the treatment of GVHD has not been fully investigated in regard to the risk of developing VTE. It is possible that unrecognized factors may also contribute to the risk of developing VTE in allogeneic transplant recipients, and this requires further study.

VTE occurring in the context of relapsing disease occurred more frequently after autologous HSCT. These events could be viewed as cancer-related or relapse-related VTE, and are less likely to be related to factors specific to high-dose therapy. Importantly, the diagnosis of VTE after autologous HSCT may be an indicator of relapsing disease.

We acknowledge some limitations of our study. Patients undergoing allogeneic HSCT were different in several respects from patients undergoing autologous HSCT, including age, diagnosis, and duration of hospital admission. Logistic regression analysis of factors predisposing to the development of VTE would be helpful, but there were insufficient non-catheter-related events to perform this analysis in our study.

It is possible that we have not accurately estimated the incidence of VTE in patients post-HSCT, due to the retrospective nature of our study. We attempted to confirm the presence of symptoms in our patients by reviewing the medical records in detail. A prospective study may be required to confirm the incidence of symptomatic VTE post-HSCT.

Finally, a potential limitation is the lack of thrombophilia data in our patients and donors; however, thrombophilic mutations were not associated with the development of VTE in one report of patients undergoing allogeneic HSCT [28]. It would therefore appear to be unlikely that underlying thrombophilia would significantly influence our results.

In conclusion, HSCT patients are at increased risk of developing VTE. An ambulatory care model of HSCT patients may decrease the incidence of VTE, but prospective comparisons are lacking. Future studies involving larger groups of patients are required to refine the incidence among VTE in HSCT patients and confirm our observations. A prospective assessment of risk factors and prophylaxis use may identify those at highest risk, establish the role for thromboprophylaxis, and provide additional insights regarding the unique mechanism of VTE following allogeneic HSCT as compared with autologous HSCT.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

References


