# Bleeding and Thrombotic Complications

40

Shruti Chaturvedi, Binsah George, and Bipin N. Savani

## 40.1 Introduction

Bleeding and thrombotic complications are an important cause of morbidity and mortality in patients undergoing HSCT. The major thrombotic complications include venous thromboembolism, such as catheter-related thrombosis, sinusoidal obstruction syndrome (SOS), and transplant-associated thrombotic microangiopathy (TA-TMA), while bleeding can involve the GI or respiratory tracts and is most common in thrombocytopenic patients or those with GVHD.

HSCT is associated with multiple risk factors for both thrombosis and bleeding including the underlying malignancy, thrombocytopenia, high-dose MAC and immunomodulatory drugs, GVHD, infections, indwelling vascular catheters, and prolonged immobilization (Gerber et al. 2008; Chaturvedi et al. 2016; Nadir and Brenner 2007). HSCT is also associated with alterations in the coagulation system with activation of endothelium-dependent coagulation factors, increase in vWF and platelet adhesion, increased thrombin generation, decreased antithrombin levels, and decreased levels of anticoagulant proteins such as protein C (Vannucchi et al. 1994). Collectively, major patient-, disease-, and therapy-related factors contribute to hemostatic complications in HSCT patients. Thrombotic and bleeding complications in HSCT are discussed separately below.

S. Chaturvedi
Division of Hematology, Department of Medicine, Johns Hopkins Hospital, Baltimore, MD, USA

B. George · B. N. Savani (✉)
Hematology and Stem Cell Transplantation Section, Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center and Veterans Affairs Medical Center, Nashville, TN, USA
e-mail: Bipin.Savani@vanderbilt.edu

## 40.2 Thrombotic Complications

### 40.2.1 Epidemiology and Risk Factors

Thromboembolic complications in HSCT recipients include venous thromboembolism (VTE), catheter-associated thrombosis (CAT), sinusoidal obstruction syndrome, and TA-TMA. VTE is the most common of these complications, and retrospective studies have reported VTE incidence as high as 4.6% over 180 days for inpatients undergoing HSCT (Gerber et al. 2008). The rate of VTE is higher with allo-HSCT than auto-HSCT and in the presence of GVHD with 1-year VTE rates of 4.8%, 6.8%, and 8.1% reported with auto-HSCT, allo-HSCT without GVHD, and allo-HSCT with GVHD, respectively (Pihusch et al. 2002). A retrospective series of 447 patients undergoing BMT reported a 5.7% incidence of VTE in the first 100 days following transplant despite being on heparin prophylaxis (100 U/kg iv daily) for hepatic SOS (Pihusch et al. 2002). Finally, Gonsalves


E. Carreras et al. (eds.), *The EBMT Handbook*, https://doi.org/10.1007/978-3-030-02278-5_40

**Table 40.1** Recommendations for prophylaxis and treatment of VTE in HSCT recipients[a]

| VTE prophylaxis | VTE treatment |
|---|---|
| *Indications for prophylaxis*<br>– Patients with MM receiving IMiDs<br>– During hospitalization or postoperatively, as long as platelet count is >50 × $10^9$/L<br>– Prophylaxis is not recommended in outpatients with indwelling vascular catheters<br>*Prophylaxis strategy*<br>– Aspirin in low-risk patients with MM receiving IMiDs<br>– LMWH (prophylactic dose of 40 mg SC daily) for patients with MM on IMiDs and >1 risk factor for VTE<br>– Prophylactic doses of UFH or LMWH in hospitalized patients | *General principles*<br>– Start therapeutic doses of LMWH or IV UFH in patients who have platelet count >50 × $10^9$/L and no active bleeding. UFH is preferred in case of renal impairment (GFR <30 mL/min) or high bleeding risk<br>– Continue LMWH or transition to warfarin (if LMWH is contraindicated) for maintenance therapy<br>– DOACs are not currently recommended in patients undergoing HSCT<br>*Duration of anticoagulation*<br>– *General*: 3–6 months or as long as malignancy or use of IMiDs persists, whichever is longer<br>– *Catheter-related thrombosis*: 3 months or as long as catheter is in place<br>*Inferior vena cava filter*<br>Only use to patients in whom anticoagulation is contraindicated or those who develop pulmonary embolism on anticoagulation. Remove as soon as anticoagulation can be started |

*DOACs* direct oral anticoagulants, *IMiDs* immunomodulatory drugs, *LMWH* low molecular weight heparin, *MM* multiple myeloma, *UFH* unfractionated heparin
[a]Adapted from Chaturvedi et al. (2016)

et al. reported a 1-year symptomatic VTE incidence of 3.7% in patients undergoing HSCT in an *ambulatory* care setting (Gonsalves et al. 2008).

VTE occurs most frequently following engraftment, in patient undergoing allo-HSCT, those with a history of previous VTE or GVHD (Labrador et al. 2013). The majority of VTE episodes in these studies were catheter-associated thrombosis. Cortelezzi et al. have previously reported that there was a 12% incidence of catheter-related thromboembolic complications in a cohort of 416 patients with hematologic malignancies (Cortelezzi 2005). Twenty-one percent of these patients were HSCT recipients, and 81.2% had platelet counts less than 50 × $10^9$/L. There was a non-statistically significant trend toward lower rates of thrombotic complications with thrombocytopenia. Prolonged hospitalization and inherited thrombophilias (e.g., factor V Leiden, prothrombin gene mutation, protein C or S deficiency) are associated with an increased risk of thrombosis in the general population and may add to thrombosis risk in the HSCT population as well.

## 40.2.2 VTE Prophylaxis

### 40.2.2.1 Randomized Studies

*Randomized studies* have not evaluated empiric prophylactic anticoagulation in HSCT recipients; however, studies in patients with cancer provide the next best evidence that can be extrapolated. The PROTECHT (nadroparin versus placebo) and SAVE-ONCO (semuloparin versus placebo) trials showed a significant reduction in the relative risk of VTE with prophylactic anticoagulation in patients with cancer; however the absolute risk reduction is small, and no survival benefit has been demonstrated. The American Society of Clinical Oncology (ASCO) guidelines advise against the use of routine prophylactic anticoagulation in ambulatory patients with cancer (Lyman et al. 2015). We do not generally recommend prophylactic anticoagulation in thrombocytopenic HSCT recipients with the exception of those with multiple myeloma (MM) receiving thalidomide or lenalidomide or hospitalized patients at higher risk of thrombosis (Table 40.1).

### 40.2.2.2 Multiple Myeloma

Patients with MM have a high baseline risk of thrombosis of 5–10% that increases several-fold in patients being treated with the immunomodulators (IMiDs) THAL and LENA with DEX or chemotherapy. Consolidation therapy with THAL or LENA after HSCT has been shown to improve CR rates and prolong EFS and is thus rapidly becoming standard of care (McCarthy et al. 2012; Barlogie et al. 2006). In patients receiving THAL consolidation after auto-HSCT for MM, the rate of VTE was 24% and 6% in the induction and consolidation periods, respectively,

despite thromboprophylaxis with low molecular weight heparin (LMWH) (Barlogie et al. 2006). McCarthy et al. reported no episodes of VTE in patients receiving consolidation therapy with LENA; however, these patients also received prophylactic anticoagulation (McCarthy et al. 2012). Based on studies showing a benefit of thromboprophylaxis in patients with newly diagnosed MM receiving LENA- or THAL-based treatment (Palumbo et al. 2011) and the ASCO recommendation for thromboprophylaxis in this population (Lyman et al. 2015), we recommend either aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients receiving THAL or LENA.

#### 40.2.2.3 Hospitalized Patients

Though there is a clear benefit of pharmacologic thromboprophylaxis in medically ill hospitalized patients (Samama et al. 1999), randomized trials have not evaluated thromboprophylaxis in HSCT patients. The potential benefit from VTE prophylaxis is proportional to VTE risk, and therefore this is particularly important in patients with reduced mobility and with a history of VTE (if not on long-term anticoagulation) due to an even higher risk of thrombosis. Our practice is to start prophylactic anticoagulation for hospitalized patients in the post transplant period once the platelet count is $>50 \times 10^9$/L and there is no active bleeding. For very high-risk patients, anticoagulation can be considered if the platelet count is $>30 \times 10^9$/L; however this must be balanced with the risk of bleeding.

#### 40.2.2.4 Prophylaxis of Catheter-Related Thrombosis

HSCT patients, especially those undergoing "ambulatory" HSCT, frequently have indwelling vascular catheters with the potential of catheter-related thrombosis (CRT). Despite multiple randomized and observational studies, thromboprophylaxis for the prevention of CRT in patients with cancer remains controversial. The largest study of thromboprophylaxis in CVC randomized 1590 cancer patients undergoing chemotherapy to adjusted-dose warfarin (international normalized ratio, 1.5–2.0), fixed-dose warfarin (1 mg/day), and no prophylaxis (Young et al. 2009). Symptomatic CRT was less frequent in the patients given adjusted-dose warfarin than in those who received no prophylaxis (2.7% vs 5.9%, $P = 0.019$); however, both adjusted-dose and fixed-dose warfarin were significantly associated with increased risk of major bleeding (Young et al. 2009). Recent meta-analyses of randomized trials concluded that prophylactic warfarin and LMWH do not significantly reduce symptomatic CRT in patients with cancer (Akl et al. 2007). Based on the available evidence, we do not routinely recommend prophylactic anticoagulation to prevent catheter-related thrombosis.

### 40.2.3 VTE Diagnosis and Treatment

Venous duplex ultrasonography should be performed in patients presenting with extremity swelling, redness or tenderness, or pulmonary angiography in patients with chest pain, dyspnea, or unexplained tachycardia. A clinical assessment of bleeding risk is necessary in patients who are diagnosed with VTE. Patients with no increased risk based on bleeding history and platelet count $>50 \times 10^9$/L should be started on therapeutic anticoagulation with either LMWH or unfractionated heparin (UFH). The use of LMWH is restricted to patients with glomerular filtration rate >30 mL/min, while UFH is used in patients with impaired renal function (glomerular filtration rate <30 mL/min) or those with high bleeding risk. Following initiation of anticoagulation with LMWH or UFH, patients may be continued on LMWH or transition to warfarin with a standard INR target of 2–3. LMWH is preferred in patients with evidence of relapsed malignancy. The direct oral anticoagulants (DOACs) have not been evaluated in HSCT recipients, and their use cannot currently be recommended outside of a research setting. The optimal duration of anticoagulation for VTE in HSCT patients has not been evaluated in prospective studies. The recommendation for patients with cancer-related VTE is anticoagulation for 3–6 months, with ongoing therapy if the malignancy persists (Lyman et al. 2015; Kearon et al. 2012). We follow an analogous strategy in HSCT patients with the caveat that extended

anticoagulation is often not feasible in patients with relapsed disease and a high likelihood of disease-related or treatment-related thrombocytopenia (Table 40.1).

The use of inferior vena cava (IVC) filters should be restricted to patients with acute deep vein thrombosis and a contraindication to anticoagulation and possibly patients who develop pulmonary embolism while on therapeutic anticoagulation (Kearon et al. 2012). IVC filters should not be used for primary prophylaxis of pulmonary embolism. In patients with large, symptomatic thrombosis and severe thrombocytopenia, we sometimes follow a strategy of platelet transfusions to reach a threshold of $50 \times 10^9$/L to allow safer anticoagulation with heparin.

### 40.2.4 Treatment of Catheter-Related Thrombosis

The rate of PE and mortality from CRT is low, and the objectives of CRT treatment are to reduce symptoms, prevent extension into more central veins, preserve access, and prevent chronic venous stenosis. There is no evidence that removal of the catheter improves outcomes. Therefore, it is reasonable to not to remove the catheter unless it is nonfunctional, no longer needed, or may be infected. Thrombus reduction by catheter-directed thrombolysis is relatively safe and effective and may be tried in an attempt to preserve the catheter. Anticoagulation is required in patients with acute CRT regardless of whether the catheter is removed (Kearon et al. 2012; Lyman et al. 2015). We prefer LMWH, though vitamin K antagonists (VKA) may be used if LMWH is contraindicated. In a prospective study of 78 patients with CRT treated with full-dose dalteparin bridged to warfarin, there were no new thrombotic events at 3 months, and 57% of catheters were still functional (Kovacs et al. 2007). The optimum duration of anticoagulation has not been evaluated in prospective studies. Current ACCP guidelines recommend anticoagulation for 3 months or until the catheter is removed, whichever is longer (Kearon et al. 2012). Several clinicians prefer to continue anticoagulation for 1–2 weeks after the catheter is removed.

### 40.2.5 Sinusoidal Obstruction Syndrome (SOS)

SOS (see Chap. 49) is a life-threatening complication that presents usually within the first 45 days after HSCT with elevated serum bilirubin levels, painful hepatomegaly, and fluid retention (Carreras, 2015). Endothelial injury of the hepatic sinusoids in SOS initiates hepatocyte injury and liver failure. SOS can occur in as high as 8–13% of HSCT recipients, and mortality is in excess of 80% (Carreras, 2015). MAC, preexisting liver disease, younger age, and poor performance status are associated with increased risk of SOS (McDonald et al. 1993). Ursodeoxycholic acid is recommended as prophylaxis for SOS in patients undergoing allo-HSCT. Anticoagulation with low-dose heparin has also been studied and is sometimes prescribed to patients undergoing auto-HSCT. Defibrotide, a pro-fibrinolytic agent, is a new agent approved for the treatment of severe SOS in both children and adults and is associated with higher rates of survival than historical controls (20–30% at day 100) (Richardson et al. 2016). Defibrotide prophylaxis has been shown to have some efficacy in preventing SOS in high-risk children, but whether this benefit translates for adults is not known.

### 40.2.6 Transplant-Associated TMA

TA-TMA (see Chap. 42) is a heterogeneous, frequently fatal disorder that occurs within 100 days after HSCT and is caused by treatment- and disease-related endothelial damage, coagulation activation, and microvascular thrombosis (Nadir and Brenner 2007). It is characterized by thrombocytopenia, microangiopathic anemia with schistocytes on the blood smear, and varying organ impairment such as renal failure and neurological symptoms. The diagnosis can be challenging since the clinical symptoms overlap with other common complications including GVHD and infections (Rosenthal, 2016). Risk factors for developing TA-TMA include exposure to calcineurin inhibitors, high-dose chemotherapy, GVHD, infections, advanced age, female

sex, and non-MAC (Elsallabi et al. 2016). Elevated levels of vWF and inflammatory mediators such as IL-1, TNF-alpha, thrombomodulin, etc. and neutrophil extracellular traps have been implicated as causing the endothelial damage in TA-TMA. Treatment of TA-TMA is mostly supportive; however, recent data show that some patients with severe TA-TMA harbor complement gene mutations and uncontrolled complement activation has been demonstrated in TA-TMA, which is a potential therapeutic target. The complement inhibitor eculizumab has been successfully used in some cases of TA-TMA (Rosenthal, 2016).

## 40.3 Bleeding Complications

Bleeding in HSCT recipients is closely associated with prolonged and severe thrombocytopenia. In retrospective studies, the rate of bleeding in HSCT recipients ranges from 15.2% to 27.1%, and life-threatening or fatal bleeding occurred in 1.1% to 3.6% of patients (Gerber et al. 2008; Pihusch et al. 2002, Labrador et al. 2013). Gerber et al. reported that the initiation of therapeutic anticoagulation during days 1–180 after HSCT was the strongest predictor of bleeding [OR 3.1 (95% CI 1.8–5.5)] (Gerber et al. 2008). Furthermore, GVHD [OR 2.4 (95% CI 1.1–3.3)] increased the risk of bleeding, while auto-HSCT (versus allo-HSCT) was protective [OR 0.46 (95% CI 0.33–0.64)]. Bleeding can take any form including GI hemorrhage in patients with GVHD of the gut, hemorrhagic cystitis in patients with genitourinary involvement by GVHD, viral reactivation, and alkylating agent therapy, or spontaneously. Diffuse alveolar hemorrhage (DAH) (see Chap. 52) is a devastating bleeding complication that occurs in 2–14% of HSCT recipients and presents with progressive hypoxia, pulmonary infiltrates, and bloody alveolar lavage (Nadir and Brenner 2007). DAH is more common in thrombocytopenic patients and those with acute GVHD, and the effects of inflammatory cytokines on the alveolar lining have been implicated. There are no evidence-based prophylactic and therapeutic strategies, reported mortality is around 80% (range 64% to 100%) (Afessa et al. 2002). Platelet transfusions, systemic corticosteroids, antifibrinolytics, and recombinant factor VIIa have all been used with inconsistent results. It is general practice to administer prophylactic platelet transfusions for platelet counts less than $10 \times 10^9$/L in patients undergoing myeloablative chemotherapy or HSCT, though the superiority of prophylactic over therapeutic platelet transfusions is supported by low- to moderate-grade evidence. Given the competing risks of bleeding and thrombosis, identifying patients at high risk for these outcomes can optimize strategies for prophylaxis. The timing of hemostatic complications is an important consideration since bleeding events are more likely to occur early in the post transplant course when patients are profoundly thrombocytopenic, while thrombotic events occur more frequently after hematopoietic recovery (Gerber et al. 2008; Labrador et al. 2013).

**Key Points**

- Hemostatic complications, including both thrombosis and bleeding, are common in HSCT recipients and contribute to morbidity and mortality.
- Indwelling vascular catheters, GVHD associated inflammation, and certain medications are important risk factors for VTE, while prolonged severe thrombocytopenia and GVHD predispose to bleeding.
- Pharmacologic thromboprophylaxis is recommended for patients with MM receiving IMiDs and hospitalized patients with platelet count $>50 \times 10^9$/L, but not for routine prophylaxis of CRT.
- LMWH (or UFH) is the treatment of choice for VTE in HSCT recipients.
- Ursodiol and defibrotide are recommended for the prevention and treatment of SOS, respectively. Defibrotide may also have a role in prophylaxis of high-risk patients.

## References


Afessa B, Tefferi A, Litzow MR, et al. Diffuse alveolar hemorrhage in hematopoietic stem cell transplant recipients. Am J Respir Crit Care Med. 2002;166:641–5.

Akl EA, Karmath G, Yosuico V, et al. Anticoagulation for thrombosis prophylaxis in cancer patients with central venous catheters. Cochrane Database Syst Rev. 2007;18:CD006468.

Barlogie B, Tricot G, Anaissie E, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. N Engl J Med. 2006;354:1021–30.

Carreras E. How I manage sinusoidal obstruction syndrome after hematopoietic stem cell transplantation. Br J Hematol. 2015;168:481–91.

Chaturvedi S, Neff A, Nagler A, et al. Venous thromboembolism in hematopoietic stem cell transplant recipients. Bone Marrow Transplant. 2016;51:473–8.

Cortelezzi A, Moia M, Falanga A, et al. Incidence of thrombotic complications in patients with hematological malignancies with central venous catheters: a prospective multicenter study. Br J Haematol 2005;129:811–7.

Elsallabi O, Bhatt VR, Dhakal P, et al. Hematopoietic stem cell transplant-associated thrombotic microangiopathy. Clin Appl Thromb Hemost. 2016;22:12–20.

Gerber DE, Segal JB, Levy MY, et al. The incidence and risk factors for venous thromboembolism (VTE) and bleeding among 1514 patients undergoing hematopoietic stem cell transplantation: implications for VTE prevention. Blood. 2008;112:504–10.

Gonsalves A, Carrier M, Wells PS, et al. Incidence of symptomatic venous thromboembolism following hematopoietic stem cell transplantation. J Thromb Haemost. 2008;6:1468–73.

Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e419S–96S.

Kovacs MJ, Kahn SR, Rodger M, et al. A pilot study of central venous catheter survival in cancer patients using low-molecular-weight heparin (dalteparin) and warfarin without catheter removal for the treatment of upper extremity deep vein thrombosis (The Catheter Study). J Thromb Haemost. 2007;5:1650–3.

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;98:437–43.

Lyman GH, Bohlke K, Khorana AA, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014. J Clin Oncol. 2015;33:654–6.

McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366:1770–81.

McDonald GB, Hinds MS, Fisher LD, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. Ann Intern Med. 1993;118:255–67.

Nadir Y, Brenner B. Hemorrhagic and thrombotic complications in bone marrow transplant recipients. Thromb Res. 2007;120(Suppl 2):592–8.

Palumbo A, Cavo M, Bringhen S, et al. Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. J Clin Oncol. 2011;29:986–93.

Pihusch R, Salat C, Schmidt E, et al. Hemostatic complications in bone marrow transplantation: a retrospective analysis of 447 patients. Transplantation. 2002;74:1303–9.

Richardson PG, Riches ML, Kernan NA, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. Blood. 2016;127:1656–65.

Rosenthal J. Hematopoietic stem cell transplantation-associated thrombotic microangiopathy: a review of pathophysiology, diagnosis, and treatment. J Blood Med. 2016;7:181–6.

Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. N Engl J Med. 1999;341:793–800.

Vannucchi AM, Rafanelli D, Longo G, et al. Early haemostatic alterations following bone marrow transplantation: a prospective study. Haematologica. 1994;79:519–25.

Young AM, Billingham LJ, Begum G, et al. Warfarin thromboprophylaxis in cancer patients with central venous catheters (WARP): an open-label randomised trial. Lancet. 2009;373:567–74.