

Review

Massimo Franchini*

Thromboembolic risk in hematological malignancies

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Abstract: There are a growing number of studies documenting that, similarly to patients with solid cancers, also patients with hematological malignancies (i.e., acute leukemia, lymphoproliferative and myeloproliferative neoplasms and plasma cell disorders) are at increased risk of thrombosis. The pathogenesis of the hypercoagulable state associated with hematological cancers is often multifactorial. Contributor factors include tumor cell-derived procoagulants, antineoplastic therapies, central venous catheters, concomitant infections and advanced age. In this narrative review, the epidemiology, pathogenesis and management of thrombosis in patients with hematological malignancies are reviewed.

Keywords: acute leukemia; lymphoma; multiple myeloma; myeloproliferative neoplasms; thrombosis.

Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication of malignancy [1]. Patients with cancer have a four- to six-fold higher relative risk of VTE than age- and sex-matched controls [2] and the overall prevalence of cancer-associated thrombosis is 15%, with rates as high as 50% in advanced metastatic cancer patients [2]. However, an underlying malignancy has been diagnosed in approximately 25% of all new cases presenting with symptomatic VTE [3]. As a consequence, VTE represents the second cause of morbidity and mortality in cancer patients [4–6]. The VTE risk in patients with hematological

malignancies has been considered lower than that in solid tumors for long time and physicians have been more concerned for bleeding rather than thrombotic complications in such patients. However, recent studies suggest that the incidence of thromboembolic events in oncohematological patients may be similar, or even higher, to that found in patients with solid cancers [7, 8]. Furthermore, the interest towards the problem of thrombotic complications in hematological malignancies has been renewed by the widespread use of central venous catheters (CVC) and the introduction of new immunomodulatory agents.

In this narrative review, we will summarize the current knowledge of the epidemiology, pathogenesis and management of thromboembolic complication of hematological malignancies. Thrombotic complications following hematopoietic stem cell transplantation are not included in this review.

Search methods

We reviewed the medical literature for published studies evaluating the thromboembolic complications in patients with hematological cancers. The PubMed electronic database was searched without temporal limits using an English language restriction. The key words used were: venous thromboembolism, pulmonary embolism, deep vein thrombosis, neoplasm, cancer, tumor, hematological malignancies, acute leukemia, lymphoma, lymphoproliferative disease, multiple myeloma, therapy, prophylaxis. References of most recent review articles on thrombosis in hematological malignancies were also cross-referenced to identify potentially relevant papers not captured in our initial literature search. Search terms were also applied to abstracts from the latest international hematological and oncological congresses.

Acute leukemia

Depending on the type of leukemia [i.e., acute myeloid leukemia (AML) or acute lymphoid leukemia (ALL)], the VTE

*Corresponding author: Massimo Franchini, MD, Director, Department of Hematology and Transfusion Medicine, Azienda Ospedaliera Carlo Poma, Mantua, Italy, Phone: +39 0376 201234, Fax: +39 0376 220144, E-mail: massimo.franchini@aopoma.it

incidence ranges from 2.1% up to 12.1% [9–11] (Table 1). For instance, a large population-based cohort study in about 8000 patients with acute leukemia, showed a 2-year VTE cumulative incidence of 5.2% in AML and 4.5% in ALL, with the majority of events recorded in the first month of diagnosis [12]. Older age, chronic co-morbidities, and CVC were significant predictors of VTE in both acute leukemia types. Notably, the development of VTE was associated with a 40% increase in the risk of dying within 1 year in patients with ALL, while a diagnosis of VTE was not associated with reduced survival in AML patients [12]. According to a meta-analysis of 17 studies, the rate of thrombosis in ALL pediatric patients was 5.2%, the majority of the events occurring during induction therapy with L-asparaginase [34]. A similar rate was found by another meta-analysis performed by the same group in adult ALL, in which an overall VTE incidence of 5.9% during remission induction therapy was reported [35]. A particular consideration deserves acute promyelocytic leukemia (APL), in which thrombosis and bleeding manifestations may occur concomitantly as a part of the same thrombo-hemorrhagic syndrome [36–39]. Patients with APL have profound abnormalities of hemostatic parameters including hypofibrinogenemia, prolonged prothrombin and thrombin time and increased circulating levels of fibrinogen-fibrin degradation products [37]. Since the introduction of therapy with all-trans-retinoic acid (ATRA), which promotes the terminal differentiation of promyelocytic blasts with the consequent rapid resolution of the coagulopathy, the outcome of APL has dramatically improved [40]. However, thrombotic events appear to be more common in APL than in other acute leukemia patients [38], with VTE rates varying, according to the study, from 5.1% to 16% [10, 13, 14]. For instance, in a prospective study conducted by Programa de Estudio y Tratamiento de las Hemopatías Malignas (PETHEMA) cooperative group, the overall incidence of thrombotic events in 921 patients enrolled was

4.1% at diagnosis and 9.3% during induction. Deep vein thrombosis were diagnosed in 17% of patients, whereas 46% were attributed to CVC insertion; myocardial infarction and cerebral stroke accounted for 9% and 12% of events, respectively [41].

The pathogenesis of thrombosis in acute leukemia is multifactorial [42]. A major determinant is represented by prothrombotic factors produced by leukemic cells, including tissue factor, cancer procoagulant and tumor-derived microparticles [43–45]. Pro-inflammatory and angiogenic factors secreted by acute leukemia cells can also promote thrombosis via downstream effects on platelets, endothelial cells and leukocytes [46]. Leukemic promyelocytes show the highest procoagulant activity and APL blast cell count correlates with thrombin generation [47]. In addition, various therapeutic measures, including L-asparaginase, high dose steroids, erythropoietic and myeloid growth factors, have been implicated in enhancing the hypercoagulable state [48]. Central venous catheters, as well as immobility during hospitalization, age and acute infections are also important cofactors that superimpose to the underlying hypercoagulable state [7].

Myeloproliferative neoplasms

Myeloproliferative neoplasms are clonal hematopoietic stem cell disorders characterized by an overproduction of terminally differentiated myeloid cells (i.e., leukocytes, erythrocytes, and platelets) in peripheral blood [49–51]. According to the World Health Organization (WHO) classification, the BCR-ABL-negative classical myeloproliferative neoplasms include primary myelofibrosis, polycythemia vera and essential thrombocythemia [52]. The discovery of the JAK2V617F gain-of-function mutation in 2005, found in 95% of patients with polycythemia vera and in approximately 50% of patients with essential thrombocythemia and myelofibrosis, represented a crucial advance in the diagnostic approach to myeloproliferative neoplasms [53, 54]. Other advances in this field were represented by the identification of the MPL515 mutations in the thrombopoietin receptor gene in approximately 5% and 10% of patients with JAK2V617F-negative essential thrombocythemia and myelofibrosis, respectively, and JAK2 exon 12 mutations in approximately 5% of JAK2V617F-negative polycythemia vera patients [55–57].

Although the outcome greatly varies among the different myeloproliferative neoplasms, being more favorable in essential thrombocythemia patients, the morbidity and mortality is strongly influenced by disease-related

Table 1 Incidence of thrombosis at the time of diagnosis in hematological malignancies.

Hematological malignancy	Incidence of thrombosis, %	References
Acute leukemia	2.1–21.1	[9–12]
– Acute promyelocytic leukemia	5.1–16	[10, 13, 14]
Myeloproliferative neoplasms	12–39	[15–17]
Lymphoproliferative neoplasms	1.5–14.6	[8, 18–20]
Plasma cell disorders		
– MGUS	6.1–7.5	[21, 22]
– Multiple myeloma	4–58 ^a	[23–33]

^aDepending on the type of chemotherapeutic regimens utilized.

hemostatic complications, mostly of thrombotic nature [49]. It has been estimated that thrombosis is present in 12%–39% of patients with polycythemia vera, 10%–29% with essential thrombocythemia and around 13% of myelofibrosis at the time of diagnosis [15–17]. Patients with myeloproliferative neoplasms are also at increased risk of recurrence: in a retrospective study in 235 polycythemia vera and 259 essential thrombocythemia patients, thrombosis recurred in 33.6% of cases, corresponding to 5.6% per year [58]. Arterial thromboses, including ischemic stroke, acute coronary syndrome and peripheral arterial thrombosis, are more frequent than venous thrombosis, accounting for approximately 60%–70% of all events. For instance, the European Collaboration on Low-dose Aspirin in Polycythemia Vera (ECLAP) showed that cardiovascular mortality (mainly coronary heart disease and non-hemorrhagic stroke) accounted for 41% of all deaths (1.5 deaths per 100 persons per year) [59]. However, the type of thrombosis (i.e., arterial or venous) greatly depends on age and gender, being abdominal venous thrombosis often a presenting feature of young women with myeloproliferative neoplasms [60]. Indeed, venous thromboses at unusual sites, such as cerebral sinus and splanchnic (i.e., Budd-Chiari syndrome and portal vein thrombosis) vessels have a high prevalence among patients with myeloproliferative neoplasms and not rarely are the presenting feature of the disease, leading ultimately to their diagnosis [16]. In a study of 139 patients with cerebral, portal, or mesenteric vein thrombosis, about 14% fulfilled criteria for having polycythemia vera or essential thrombocythemia at time of presentation, about 95% of which were *JAK2V617F* positive [61]. Interestingly, 43% of patients with portal, 21% with abdominal and 5% with cerebral venous thrombosis were *JAK2* positive with no other findings of myeloproliferative neoplasms. In a recent meta-analysis, a higher prevalence of *JAK2V617F* mutation and myeloproliferative neoplasms was found in patients with Budd-Chiari syndrome compared with those with portal vein thrombosis, being polycythemia vera more prevalent in the first group [62]. In a study of 707 patients with myelofibrosis, the overall rate of cardiovascular death and non-fatal thrombotic complications was 7.2% (1.75 events per 100 patient years), and the presence of *JAK2V617F* was significantly associated in the multivariate analysis [63]. Finally, three independent meta-analyses showed that the presence of *JAK2V617F* mutation in patients with essential thrombocythemia is associated with an approximately two-fold increased risk of thrombosis [64–66]. However, as for the other hematological malignancies, the interaction of genetic with acquired (i.e., age >60 years, history of prior thrombosis, cardiovascular risk factors including

hypertension and diabetes, leukocytosis) factors results in a higher thrombotic risk in patients with myeloproliferative neoplasms [67].

The pathogenesis of thrombosis in myeloproliferative neoplasms is multifactorial and involves both abnormalities of blood cells derived from the malignant clone and an inflammatory response [49, 50]. The alteration of circulating transformed blood cells (i.e., platelets, erythrocytes and leukocytes) regard not only quantitative changes in their number, with consequent hyperviscosity, but also qualitative changes leading to a prothrombotic phenotype. The latter include the production of procoagulant molecules, including microparticles, secretion of inflammatory cytokines and expression of cell adhesion molecules. Notably, P-selectin (a marker of platelet activation) has been positively correlated with the presence of *JAK2V617F* mutation [68] and a direct correlation between such mutation and platelet-associated thrombin generation has been recently described [69]. In addition, the endothelial damage caused by hyperviscosity and leukocyte-derived proteases significantly contributes to enhance the thrombotic potential in myeloproliferative neoplasms [49, 50].

Lymphoproliferative neoplasms

A number of studies have documented that the incidence of thromboembolic complications in lymphoproliferative diseases is increasing, with rates similar to those observed in patients with solid cancers [18]. The analysis of the published literature data shows that the VTE risk in patients with such conditions ranges from 1.5% to 14.6%, depending on the types of the studies, the types and stages of the diseases and the different chemotherapeutic protocols [8]. The thrombosis incidence is much higher in central nervous system lymphomas (i.e., 59.5%), as observed also in other brain tumors [70]. Two studies have prospectively evaluated the VTE incidence in patients with lymphoma [18, 19]. The first study, performed in ambulatory patients who were initiating a new chemotherapy regimen, found a VTE rate of 8.16% in Hodgkin's disease and 1.5% in non-Hodgkin's lymphoma [18]. In the other prospective study, conducted in 953 patients with high-grade non-Hodgkin's lymphoma, a 6.6% incidence was reported [19]. Mohren and colleagues [20] found an overall thromboembolic event incidence of 7.7% in 1038 treated lymphoma patients with a statistically significantly higher incidence in high-grade than in low-grade lymphoma. This finding, along with the fact that most patients had their thrombotic event

during or after chemotherapy, further confirm the key role of histotype and chemotherapy in triggering thrombotic events in patients with lymphoproliferative disease. Finally, a registry-based analysis performed in California, which analyzed 16,755 cases of non-Hodgkin's lymphoma, found a 4.0% 2-year cumulative incidence of acute VTE, which was also a strong predictor of decreased survival [71]. As regards the pathogenesis of thrombosis in lymphoma, it has been observed that, besides the classical conditions (immobility, infections, age, CVC, chemotherapy, use of hematopoietic growth factors) [7], a mediastinal mass could be an additional risk factor for VTE [72]. The increased tissue factor expression in the mononuclear cells, stimulated by the secretion of cytokines from lymphoma cells, could also contribute to the enhanced hypercoagulable state seen in patients with advanced lymphoproliferative disease [73].

Plasma cell disorders

An increased VTE risk has also been observed in patients with monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma [23, 74–76]. For instance, the incidence of thrombosis in patients with MGUS was 6.1% in a prospective analysis of 310 individuals [21] and 7.5% in a retrospective study with 174 patients [22]. Another, more recent, retrospective cohort study conducted in Italy on 1491 MGUS patients found that the VTE risk increased when the serum monoclonal protein concentration exceeded 16 g/L [77]. Two large population-based studies were performed to better define the thrombotic risk in MGUS and multiple myeloma [78, 79]. In the US Veteran Affairs Hospital study including more than 4 million adult male military veterans hospitalized between 1980 and 1996, DVT was diagnosed in 31 of 2374 MGUS cases and in 151 of 6192 multiple myeloma patients, resulting in DVT incidence of 3.1 and 8.7 per 1000 person year, respectively [78]. Thus, the incidence of DVT in multiple myeloma patients was nearly three-fold higher than in MGUS, and the risk of DVT was 3.3-fold and 9.2-fold increase in MGUS and multiple myeloma patients, respectively, compared with the general population [78]. In a Swedish study conducted in 5326 MGUS patients and 18,627 multiple myeloma patients diagnosed from 1958 to 2006, those with MGUS showed a higher risk of VTE and a slight increase of arterial thrombosis compared to a matched control group: hazard ratios at 1 and at 10 years were 3.4 and 2.1 for VTE and 1.7 and 1.3 for arterial thrombosis [79]. Interestingly, only IgG and IgA MGUS (but not

IgM) had an increased risk of thrombosis and the levels of the monoclonal protein did not affect thrombotic risk. An even higher risk was observed for multiple myeloma (hazard ratios at 1 and at 10 years were 7.5 and 4.1 for VTE and 1.9 and 1.5 for arterial thrombosis).

The introduction of the immunomodulatory agents thalidomide and lenalidomide has significantly improved the efficacy of anti-myeloma treatment but has been associated with an increased risk of VTE [75, 80]. While the risk of thrombosis is low (<5%) when these drugs are used as single-agent therapy [24–27], several studies have shown that the incidence of thrombosis markedly increases when they are administered in combination with steroids [23, 28]. Indeed, in newly diagnosed myeloma patients treated with thalidomide and high-dose dexamethasone the incidence of VTE increased up to 26% [29]. Similarly, two multicenter randomized phase III trials [30, 31] comparing lenalidomide plus dexamethasone versus dexamethasone alone in relapsed/refractory multiple myeloma patients showed a higher VTE incidence in the lenalidomide arm (VTE rate of 14.7% vs. 3.4% in the study conducted in North America [30] and 11.4% vs. 4.6% in the international study [31]). A meta-analysis of 3322 patients treated on thalidomide clinical trials revealed a 2.1-fold increased risk of VTE compared to those not treated with thalidomide and showed a greater risk in combination with dexamethasone [32]. Notably, the association of thalidomide with doxorubicine and dexamethasone further increases the risk of DVT to 58% in newly diagnosed patients [33]. Treatment with the recently introduced proteasome inhibitor bortezomib has not been associated with an increased incidence of VTE [81].

Similarly to the other hematological malignancies, general risk factors (i.e., age, cardiovascular risk factors, immobility, infections) play an important role in the pathogenesis of thrombosis in multiple myeloma. Beside paraprotein-related hyperviscosity, a key disease-specific mechanism leading to hypercoagulability includes a hypofibrinolytic state, which is thought to be produced by interactions between malignant plasma cells, marrow stromal cells, and endothelial cells, mediated by inflammatory cytokines, the most relevant being interleukin-6 and vascular endothelial growth factor (VEGF) [82]. Moreover, high levels of monoclonal protein may affect fibrin polymerization and fibrinolysis, as the abnormal fibrin structure interferes with the binding site for plasmin and factor XIII, which in turn causes an abnormal clot retraction and formation of clots more resistant to fibrinolysis [83]. Elevations of factor VIII, von Willebrand factor and fibrinogen have also been reported both in vitro studies and in patients with multiple myeloma [84]. The hemostatic

equilibrium between procoagulant and anticoagulant factors may be further unbalanced in multiple myeloma patients by defective natural anticoagulant mechanisms. Impaired protein C activity, due to an acquired resistance to activated protein C, has been reported in patients with multiple myeloma with prevalence up to 23% [85]. Finally, the direct injury to the endothelium, either by tumor cells or by chemotherapy, may further enhance the hypercoagulable state of multiple myeloma by up regulation of adhesion molecules with consequent interaction between tumor cells and endothelial cells, leukocytes and platelets and localization of tumor cell-derived thrombogenic peptides [84].

Management of thrombosis

Prophylaxis of thrombotic complications remains a challenging issue in patients with oncohematological disorders due to their high incidence of thrombocytopenia and hemorrhagic complications. Most data on the prevention of thrombosis in patients with hematological cancers come from studies in multiple myeloma patients, where the increased thrombotic rate observed after the introduction of immunomodulatory agents required the introduction of thromboprophylaxis, at least in the first 4–6 months of therapy [86, 87]. A number of trials have investigated the role of thromboprophylaxis with low molecular weight heparin (LMWH), warfarin and acetyl salicylic acid (ASA) in multiple myeloma patients [33, 88–90]. In particular, two randomized clinical trials on optimal thromboprophylaxis in multiple myeloma were recently published [91, 92]. In the first trial, 667 previously untreated multiple myeloma patients receiving thalidomide-containing regimens, with no clinical indication or contraindication for antiplatelet or anticoagulant therapy, were randomized to receive ASA (100 mg/day), warfarin (1.25 mg/day) or enoxaparin (40 mg/day) for the duration of induction therapy [91]. A total of 43 of the patients (6.5%) experienced a serious thromboembolic event with no significant differences in their incidence among the LMWH (3.2%), ASA (5.9%) and warfarin (8.2%) groups. In elderly patients warfarin was less effective than LMWH. The second study included 342 multiple myeloma patients that received four cycles of lenalidomide–dexamethasone as induction and were randomized to either aspirin (100 mg/day) or enoxaparin (40 mg/day) [92]. Based on seven VTE events, the incidence of VTE was not statistically different between the arms, being 2.3% in the aspirin group and 1.2% in the LMWH group. Thus, based on the guidelines published in 2008 by the

International Myeloma Working Group [87] on the prevention of VTE in multiple myeloma patients treated with thalidomide or lenalidomide, prophylactic doses of LMWH (or full intensity warfarin anticoagulation with an INR between 2 and 3) are recommended for patients treated with high dose dexamethasone, doxorubicin or multiagent chemotherapy or when more than one risk factor for VTE is present (i.e., age, obesity, CVC, co-morbidities such as diabetes, infections or cardiovascular diseases, immobility, history of VTE, inherited thrombophilia and myeloma-related hyperviscosity): these patients are considered at high risk of developing thrombotic events. Aspirin is recommended in low-risk patients, i.e., those with one or no risk factor [87]. As the thrombotic risk is greater in the first 6 months from diagnosis, a 6-month prophylaxis seems to be justified [42].

Prophylaxis with low-dose ASA (100 mg/day) is also recommended for all polycythemia vera patients, on the basis of the results of the European Collaboration on Low-dose Aspirin in Polycythemia Vera (ECLAP) trial, which demonstrated that ASA significantly reduces thrombotic events (RR=0.40; 95% CI 0.18–0.91; p=0.0277) [93]. The clinical utility of ASA prophylaxis in patients with essential thrombocythemia is less established, due to the lack of randomized clinical trials and considering also that patients with a platelet count $<1.500 \times 10^9/L$ are

Table 2 Prevention and treatment of thromboembolic complications in patients with oncohematological disorders.

VTE management	Recommendation	References
Prophylaxis		
– Multiple myeloma	Patients treated with thalidomide or lenalidomide: Low-risk patients: low-dose ASA (100 mg/day) for 6 months ^a High-risk patients: LMWH or warfarin (INR 2–3) for 6 months ^a	[87]
– Polycythemia vera	Low-dose ASA (100 mg/day)	[93]
– Essential thrombocythemia	Low-dose ASA (100 mg/day) in patients with microvascular symptoms	[96]
Treatment	LMWH for at least 6 months	[97]

ASA, acetyl salicylic acid; INR, international normalized ratio; LMWH, low molecular weight heparin; VTE, venous thromboembolism. ^aAccording to the guidelines from the International Myeloma Working Group on the prevention of VTE in multiple myeloma patients treated with thalidomide or lenalidomide [86], high-risk patients are those treated with high dose dexamethasone, doxorubicin or multiagent chemotherapy or those with more than one risk factor for VTE. Low-risk patients are those with one or no risk factor.

at increased bleeding, rather than thrombotic, risk [94, 95]. Low-dose ASA is actually recommended in essential thrombocythemia patients with microvascular symptoms, including erythromelalgia and transient neurological and ocular disturbances [96].

Similarly, very limited experience is currently available in the literature on the treatment of thromboembolic events in patients with hematological malignancies. Thus, according to the clinical experience in patients with solid cancer, monotherapy with LMWH for at least 6 months is actually recommended for patients with hematological neoplasms and an established VTE [46]. Indeed, LMWH has been demonstrated to be superior to warfarin for the secondary prevention of VTE in cancer patients [97]. Table 2 summarizes the current approach to prevention and treatment of thrombosis in patients with hematological cancers.

Conclusions

Patients with hematological malignancies have profound abnormalities of the hemostatic system, predisposing them to an increased hemorrhagic and thrombotic risk. In particular, thromboembolic events have a significant impact on morbidity and mortality of patients with oncohematological disorders. However, in spite of the burden of the problem, very little clinical experience exists on the management of thrombotic complications in such patients, with the exception of multiple myeloma setting. Randomized controlled trials are urgently needed to compare the efficacy and safety of the various antithrombotic agents in order to provide guidelines with recommendations on the best prophylactic and therapeutic approach to VTE in the setting of hematological malignancies.

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