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EDITED BY
Zsuzsa Bagoly,
University of Debrecen, Hungary

REVIEWED BY
Valentina Giudice,
University of Salerno, Italy
Danilo De Novellis,
Ospedali Riuniti San Giovanni di Dio e Ruggi d'Aragona, Italy

*CORRESPONDENCE
Jahan Abdi
jabdi@csudh.edu

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Abnormalities of primary and secondary hemostasis in multiple myeloma: insights from studies on thrombopoiesis, the coagulation system, and the bone marrow microenvironment

Jahan Abdi* and Payman Nasr

Department of Clinical Science, College of Health, Human Service and Nursing (CHHSN), California State University Dominguez Hills, Carson, CA, United States

In multiple myeloma (MM), hemostatic disorders such as thrombocytopenia, coagulopathies, and thrombophilia are well-documented. These abnormalities can be partially attributed to therapy, including thrombocytopenia following treatment with proteasome inhibitors such as bortezomib and carfilzomib or thrombosis associated with immunomodulatory drugs such as thalidomide and lenalidomide. However, acquired hemostatic disorders have also been observed in untreated or newly diagnosed MM patients. This review explores these abnormalities in both treated and untreated contexts, presenting recent studies that provide new insights into the mechanisms underlying these complications. It highlights the role of the bone marrow microenvironment, particularly mesenchymal stromal cells (MSCs) and extracellular vesicles (EVs). Additionally, the review discusses future research directions on hemostatic disorders, including bleeding and thrombosis, in MM patients. Overall, this review aims to be a valuable resource for scientists and clinicians in the field.

KEYWORDS

multiple myeloma, coagulopathy, bone marrow mesenchymal stromal cells, bleeding diathesis, thrombosis

Introduction

Multiple myeloma (MM) is a hematologic neoplasm primarily confined to the bone marrow, characterized by a dominant clone of malignant plasma cells and presenting with hypercalcemia, renal failure, anemia, and bone lesions (1). Abnormalities in both primary and secondary hemostatic systems are significant challenges in the clinical management of MM patients. For instance, thrombocytopenia is a common and often unavoidable complication associated with drug treatments (2, 3). Additionally, MM can negatively impact normal thrombopoiesis, platelet function, and the coagulation process (4, 5).

Understanding the molecular mechanisms underlying these abnormalities is crucial for advancing knowledge of MM pathophysiology. This understanding can aid in identifying new therapeutic targets and developing improved clinical management strategies to reduce the risk of serious complications. Early studies and recent research have provided insights into the impact of paraproteins on coagulation factors, the effects of MM tumor cells on platelet production and function, and the role of the bone marrow microenvironment in impaired thrombopoiesis in MM (5–7).

Despite these advances, gaps remain in our understanding of how the MM oncogenic process disrupts normal hemostasis. Further research is needed to elucidate these mechanisms and improve patient outcomes.

Therapy-related hemostatic abnormalities

Thrombocytopenia

Chemotherapy-related thrombocytopenia is common in hematologic malignancies, including MM. Mellors et al. conducted a retrospective study on MM patients treated with chemotherapy over 11 years and found that 18% developed thrombocytopenia, which was correlated with lower overall survival (OS) and progression-free survival (PFS) (2). Shaw et al. reported that thrombocytopenia incidence was higher in hematologic malignancies than in solid tumors, with the highest rate in MM patients (37.7%) (3). In relapsed or refractory MM patients, the combination of daratumumab with bortezomib or dexamethasone resulted in grade 3 or 4 thrombocytopenia in 45.3% of cases, though it also prolonged PFS (8). Thrombocytopenia was also observed in patients treated with teclistamab, a bispecific antibody that targets both T cells and MM cells (9). The exact mechanisms—whether due to drug toxicity on thrombopoiesis, altered platelet release dynamics, or direct platelet toxicity—remain unclear.

Bortezomib-induced thrombocytopenia is unique in its cyclic pattern and kinetics. Bortezomib-related thrombocytopenia typically appears within the first 10 days of each treatment cycle, with a short recovery time and no cumulative or persistent effects. This is reported to be due to a functional alteration in platelet budding (proplatelet formation) rather than marrow megakaryocyte (MK) toxicity (10). Apparently, inhibition of NFκB activity by proteasome inhibitors (PIs) (11–13) underlies this effect, as NFκB activity is crucial for platelet budding and function (14–17). The cyclic nature of bortezomib-related thrombocytopenia was later demonstrated in Murai's study in a mouse model, which showed that platelet count declined on days 2-4 post-administration and recovered to the normal range on day 6, however, proplatelet formation was significantly decreased without affecting bone marrow MKs or their ploidy distribution (18). Further studies confirmed that proteasome inhibition disrupted proplatelet formation in human and mouse MKs (19), and mice deficient in the proteasome subunit PSMC1 (26S protease regulatory subunit 4) exhibited severe thrombocytopenia and early mortality (19). Digital modeling also suggested that pan-proteasome inhibitors (bortezomib, carfilzomib, and ixazomib) promoted thrombocytopenia via myelosuppression or inhibition of (pro-)platelet formation (20). Additionally, Baaten et al. found that MM patients treated solely with alkylating agents who developed severe thrombocytopenia (<50×10^3/μL) had impaired mitochondrial function, highlighting a different mechanism of drug-induced thrombocytopenia (21).

Thalidomide, an immunomodulatory drug (IMiD), is associated with thrombocytopenia in MM, potentially through immune-mediated mechanisms that trigger platelet destruction. Keshava-Prasad et al. reported a case of thalidomide-induced thrombocytopenia with increased mean platelet volume (MPV) and elevated MKs in the bone marrow, suggesting an immune cause for the low platelet count (<20×10^3/μL) as no other factors were identified (22). Ryuge et al. documented a case of immune thrombocytopenic purpura (ITP) in an MM patient on a thalidomide regimen and indicated that the drug might have modulated normal lymphocytes to produce autoantibodies against platelets (23). In addition, a more recent case report described a 59-year-old MM patient who developed ITP following lenalidomide treatment but responded well to standard ITP therapy with intravenous immunoglobulin (IVIG) (24). These findings support an immune mechanism underlying IMiD-related thrombocytopenia in MM.

While thalidomide and lenalidomide are more commonly known to predispose MM patients to thrombotic events, thrombocytopenia remains an unavoidable, mostly transient, complication of IMiD therapies in MM. A collective evaluation of previous reports to date suggests that an autoimmune response results in the destruction of platelets and the development of ITP in some MM patients on IMiD therapy. Recognizing this potential side effect, it is crucial for clinicians to monitor and manage patients appropriately, adjust treatment regimens, and provide supportive care as needed.

Thrombophilia (hypercoagulability)

Thrombosis risk factors include hereditary gene mutations, acquired factors such as surgery, a sedentary lifestyle, and advanced age. Both the oncogenesis process in cancer and cancer chemotherapy predispose patients to thrombosis (25). New treatments, including PIs, IMiDs, and monoclonal antibodies, have significantly improved the clinical outcomes for MM patients (26) but have also increased the frequency of thrombotic events, becoming a major cause of morbidity and mortality (mostly IMiDs and some PIs) (27–37). Thalidomide and lenalidomide are particularly associated with a heightened risk of thrombosis, especially when combined with high-dose dexamethasone and other chemotherapy (38, 39). Thrombotic incidence can reach up to 26% in some studies (40–42), with hemostatic changes often developing during the first month of thalidomide and dexamethasone therapy (43). Furthermore, venous thromboembolism (VTE) and arterial

thrombosis in MM patients correlate with higher mortality rates compared to those without thrombosis (28). Thalidomide was FDA-approved in 2006 for use with high-dose dexamethasone in newly diagnosed MM, although the first reports of thalidomide-related deep vein thrombosis (DVT) in MM patients treated with this combination appeared in 2001 (44). Table 1 provides further information related to drug-associated thrombotic events in MM.

Thrombomodulin, a cofactor for thrombin in activating protein C and inhibiting coagulation, undergoes transient reduction during initial therapy, potentially increasing thrombotic risk (45, 46). Certain drugs such as thalidomide derivatives enhance myelopoiesis but downregulate PU.1 transcription factor, promoting promyelocyte accumulation and increased cathepsin G, a potential thrombotic risk (47).

TABLE 1 Drug-related thrombotic events reported by clinical studies that used IMiD and/or PI treatment modalities.

Drug category	Treatment modality	Clinical study	Comments	Reference
IMiDs	Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone	Randomized controlled trial	Risk of VTE 1-2% during frontline therapy	(27)
IMiDs	Melphalan and prednisone versus melphalan, prednisone and thalidomide	Meta-Analysis	Odds ratio for VTE was 2.4, in favor of melphalan-prednisone	
IMiDs	Pomalidomide alone or in combination with dexamethasone	Multicenter, open-label, randomized phase II study	This study showed a lower rate of VTE Fewer data available regarding thrombogenic potential	
PIs	Carfilzomib with lenalidomide and dexamethasone (carfilzomib group) or lenalidomide and dexamethasone alone (control group)	Randomized controlled trial (ASPIRE investigators)	Incidence of VTE was 13% in the patients treated with carfilzomib, lenalidomide and dexamethasone vs 6% in those who received only lenalidomide and dexamethasone	
IMiDs	Lenalidomide in combination with doxorubicin or with other chemotherapies such as adriamycin, doxorubicin, or cyclophosphamide	Retrospective cohort study on US veterans	The study showed that VTE during the first 6-12 months of therapy was associated with increased mortality	(28)
IMiDs	Cyclophosphamide, vincristine, doxorubicin, and dexamethasone (CVAD) induction group vs cyclophosphamide, thalidomide, and dexamethasone (CTD) group.	Myeloma IX and Myeloma XI phase 3 randomized controlled trials for newly diagnosed multiple myeloma (NDMM)	In Myeloma IX, risk of VTE was higher in transplant-eligible patients assigned to CVAD induction compared to those in the CTD arm. For transplant-ineligible patients, VTE risk was higher in attenuated CTD (CTDa) induction arm compared to the melphalan and prednisolone (MP) arm. In Myeloma IX, risk of VTE was higher in transplant-eligible patients randomly assigned to CVAD induction compared to those in the CTD arm. For transplant-ineligible patients, VTE risk was higher in attenuated CTD (CTDa) induction arm compared to the melphalan and prednisolone (MP) arm. In Myeloma XI, VTE risk was the same for patients under cyclophosphamide, lenalidomide, and dexamethasone (CRD) or CTD treatments (transplant-eligible), and for those under attenuated CRD (CRDa) or CTDa treatments (transplant-ineligible). Thrombotic events occurred almost entirely within 6 months of treatment initiation.	(29)
IMiDs	Lenalidomide plus dexamethasone	Safety study	The study was performed on 50 patients with recurrent MM, 10% developed VTE	(30)
PIs	Bortezomib vs high-dose dexamethasone in patients with relapsed MM	Randomized (1:1), open-label, phase 3 study (APEX investigators)	The study treated 669 patients with relapsed MM with bortezomib followed by high-dose dexamethasone. No thrombotic event was reported	(31)
PIs	Bortezomib plus Melphalan and Prednisone	Phase 3 trial (VISTA investigators)	The study treated 682 MM patients with melphalan and prednisone either alone or combined with bortezomib. It reported a very low VTE rate.	(32)
IMiDs	Lenalidomide plus dexamethasone	Open label randomized controlled trial	The study reported 26% deep vein thrombosis (DVT) in Len + high dose dexamethasone. They also concluded that lenalidomide plus low-dose dexamethasone	(34)

(Continued)

TABLE 1 Continued

Drug category	Treatment modality	Clinical study	Comments	Reference
			was associated with better short-term overall survival and with lower toxicity.	
PIs+IMiDs	Bortezomib, Lenalidomide, Dexamethasone (RVD) or Carfilzomib, Lenalidomide, Dexamethasone (KRD) with Aspirin or Rivaroxaban Thromboprophylaxis	Single-center retrospective study	A retrospective study of 305 newly diagnosed MM patients who received RVD or KRD with thromboprophylaxis. VTE rates in KRD + aspirin, RVD + aspirin, and KRD + rivaroxaban were statistically significant, 16.1%, 4.8%, and 4.8%, respectively. This study also shows the advantage of rivaroxaban prophylaxis vs aspirin.	(35)

Platelet activation significantly contributes to thrombophilia in various conditions including myeloproliferative neoplasms (48) and COVID-19 (49). IMiDs, particularly thalidomide, have been linked to platelet activation and thrombotic events in MM patients. Thalidomide increases CD62P expression and PLA (platelet-leukocyte aggregate) formation in MM patients (50), markers associated with thrombosis and cardiovascular disease in humans (51, 52). Further studies demonstrate that IMiDs induce procoagulant activity (PCA) in MM by enhancing tissue factor exposure and phosphatidylserine (PS) on monocytes and endothelial cells (53). Using flow cytometry and confocal microscopy, Guo et al. found a significantly higher percentage of PS+ blood cells in MM patients vs healthy donors. In their *in vitro* studies, incubation of endothelial cells or blood cells with MM patient's serum or with IMiDs and dexamethasone increased PS exposure on these cells (54). Finally, IMiDs also elevate plasma levels of hemostatic markers in MM patients, suggesting a hypercoagulable state (55).

Proteasome inhibitor-related thrombosis has also been reported in MM. While bortezomib has been associated with a low risk of thrombosis, it has been able to confer some level of protection against thrombosis if combined with IMiDs the mechanism of which is unclear (56). On the contrary, carfilzomib, especially in combination with dexamethasone, has been associated with increased incidence of thrombotic events in some clinical trials including ENDURANCE (57). The study by Alanazi et al. suggested enhanced platelet activation and increased platelet adhesion to type I collagen as the mechanisms underlying this carfilzomib effect (58). Additionally, a very recent study identified a germline mutation in the factor H gene as the cause of complement system dysregulation, hence an explanation for thrombotic microangiopathy (TMA) in MM patients following carfilzomib treatment (59).

Incidence of DVT associated with old doxorubicin-based regimens in MM was also reported (60, 61), which could be (at least partly) due to increased exposure of PS on platelets or increased generation of PS-exposing platelet microparticles by doxorubicin (62).

Findings from all the above studies indicate that IMiDs and chemotherapy might promote or pave the way for the development of thrombosis in MM mainly through interaction with components of the hemostatic system including endothelial cells, platelets and coagulation pathways.

Hemostatic abnormalities unrelated to therapy in MM

Impaired thrombopoiesis: role of the bone marrow microenvironment

The bone marrow microenvironment in MM is a complex network of hematopoietic and non-hematopoietic cells, including stromal cells, macrophages, adipocytes, and endothelial cells, along with extracellular matrix proteins. This milieu serves as a protective niche for MM cells, promoting their proliferation, protecting against treatment, and contributing to bone lesions (63).

Thrombocytopenia is relatively uncommon in MM at diagnosis despite significant marrow infiltration. This phenomenon may be partly attributed to the thrombopoietic activity of interleukin-6 (IL-6) and elevated levels of thrombopoietin (TPO), two cytokines secreted by bone marrow mesenchymal stromal cells (MSCs) (64, 65). Studies indicate that while IL-6 supports normal platelet counts in newly diagnosed MM, elevated TPO levels are more indicative of disease progression rather than active thrombopoiesis, potentially reflecting a disrupted regulatory role in the bone marrow microenvironment (66–68).

TPO exerts its effects through binding to its receptor c-MPL on MK progenitors, regulating platelet production (69). In MM, there is no reported genetic mutation affecting c-MPL function, suggesting normal receptor activity despite thrombocytopenia. Clinical trials with Eltrombopag, a non-peptide TPO agonist, have shown promise in increasing platelet counts in MM patients (70, 71), further indicating multifactorial mechanisms in MM-associated thrombocytopenia.

Bone marrow MSCs, pivotal in supporting hematopoiesis, including thrombopoiesis (72–74), demonstrate altered functions in MM (75–78). These MSCs may contribute to impaired thrombopoiesis through dysregulated cytokine production, such as transforming growth factor-beta (TGFβ) (79), which inhibits hematopoiesis and promotes MM progression (80–82). In MM, TGFβ also enhances osteoclast activity, contributing to bone lesions (83). Furthermore, MSCs in MM display distinct transcriptomes and cytokine profiles compared to their normal counterparts (77, 78). This altered phenotype may disrupt interactions with hematopoietic stem cells (HSCs), progenitors, and MKs,

potentially influencing MK function and platelet production in MM.

Interleukin-8 (IL-8), elevated in MM patients, inhibits normal megakaryopoiesis and is associated with bone lesions and altered responses to immune treatments (84–86). The inhibitory effects of IL-8 on normal megakaryopoiesis were shown in early studies in which IL-8 inhibited MK colony formation or maturation (87, 88). Thus, MSCs in MM may contribute to thrombopoiesis dysregulation through IL-8 and other cytokines, influencing disease pathogenesis and therapeutic responses. A postulated mechanism for MSC-mediated impairment of thrombopoiesis in MM is presented in Figure 1.

Impaired thrombopoiesis: role of extracellular vesicles (exosomes)

Exosomes, small (30-150nm) extracellular vesicles (EVs) of endosomal origin, play crucial roles in normal and malignant hematopoiesis by transferring mRNAs, miRNAs, and proteins between cells. They are secreted by various cell types, including immune cells, MSCs, and tumor cells, influencing diverse cellular processes such as signaling pathways, proliferation, and migration (89).

Numerous studies have demonstrated the role of exosomes in drug resistance, angiogenesis, immune suppression, and bone lesions of MM (89). Roccaro et al. showed that exosomes released from bone marrow MSCs and transferred to MM cells play a role in disease progression. Specifically, they found a lower concentration of the tumor suppressor miR-15a and a higher concentration of CCL2, IL-6, γ-catenin, and fibronectin in exosomes derived from BM-MSCs of MM patients compared to exosomes derived from normal BM-MSCs (90).

Exosomes not only affect tumor cells directly but also modulate interactions between malignant cells and healthy hematopoietic stem and progenitor cells (HSPCs) within the bone marrow niche. They may impair normal hematopoiesis by reducing the viability and colony formation of HSPCs, particularly affecting late progenitors such as common myeloid progenitors (CMPs), megakaryocyte-erythroid progenitors (MEPs), and B and natural killer (NK) progenitors (91). Notably, elevated levels of miRNAs such as miR-34a, miR-150, miR-155, and miR-21 in HSPCs treated with MM-derived exosomes suggest a regulatory role in MK

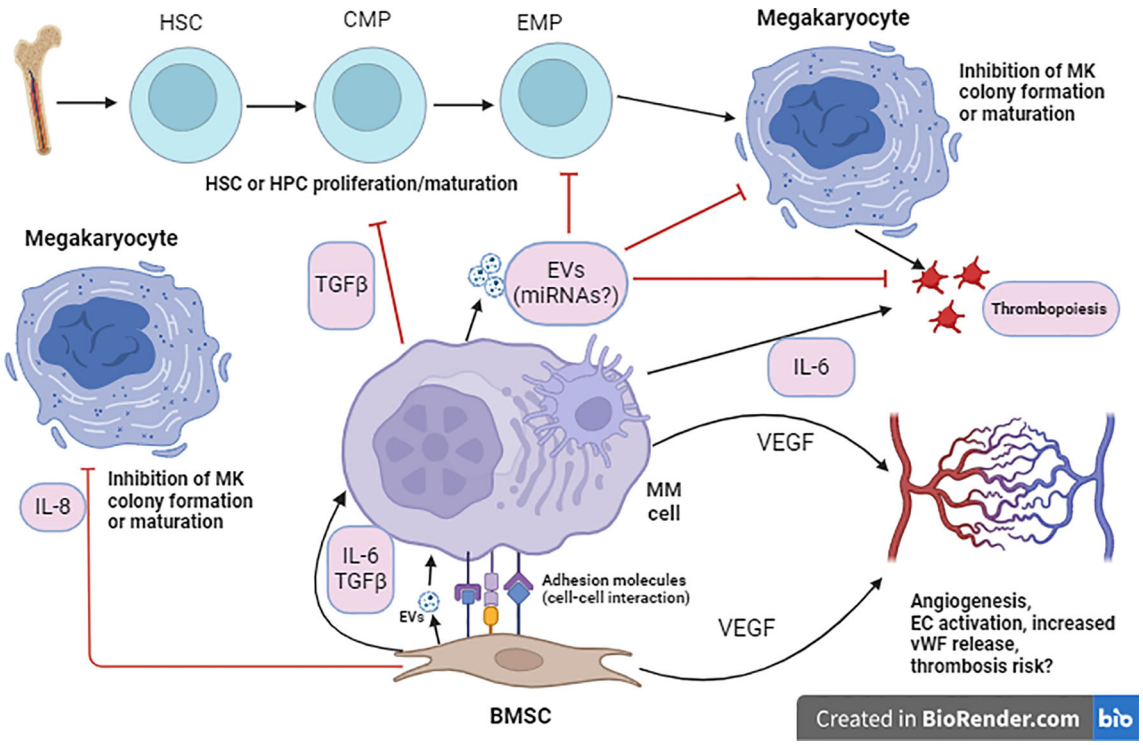

FIGURE 1
Proposed cellular interaction model for MSC-mediated impaired thrombopoiesis in MM. Within the BM microenvironment, MSCs enhance proliferation and survival of MM cells through direct adhesion (adhesion molecule signaling) or indirectly through secretion of cytokines such as IL-6 or TGFβ. Such interaction also indues secretion of cytokines such as IL-6 and extracellular vehicles (EVs) by MM cells which could, respectively, induce thrombopoiesis or suppress thrombopoiesis (through inhibition of MK colony formation and maturation) and platelet function. EVs are known to affect target cells by releasing their miRNA cargo. MM cells may interact with HSCs or HPCs (hematopoietic progenitor cells) and inhibit their proliferation or differentiation through cytokines such as TGFβ. MSCs can also secrete VEGF (vascular endothelial growth factor) which induces proliferation of ECs (endothelial cells) and angiogenesis. Another cytokine which may mediate MSC-mediated suppression of MK colony formation and maturation is IL-8. Note: It is important to mention that a plethora of cytokines is involved in the interaction between MSCs and MM cells, only cytokines related to the context are shown here.

development. For instance, overexpression of miR-155 in K562 cells blocked differentiation of these cells to MK (92), and significantly reduced the number of MKs *in vivo* (93). miR-155 levels decreased during megakaryopoiesis in cultured human cord blood and overexpression of miR-155 impaired MK proliferation and development (94). However, increased levels of miR-34a and miR-150 favored MK proliferation and differentiation in other studies (95, 96), and miR-21 deletion significantly reduced the frequencies of CMPs, MEPs, and common lymphoid progenitors in the BM *in vivo* (97). These findings underscore the complex regulatory mechanisms mediated by exosomal miRNAs in MM-associated thrombopoiesis.

Of note, exosomes have heterogeneous effects on hematopoiesis in other malignancies as well. In acute myeloid leukemia (AML), EVs impair HSPC clonogenicity and induce quiescence (98), while in myelodysplastic syndromes (MDS), they exhibit contrasting effects, enhancing HSPC viability and clonogenicity (99) or inducing apoptosis and DNA damage (100). These discrepancies highlight the context-dependent nature of EV-mediated effects on hematopoiesis, influenced by different malignancies, EV isolation techniques, and the heterogeneity of EV populations.

Impaired thrombopoiesis: the role of other factors

In MM, thrombocytopenia is not solely attributed to marrow infiltration by malignant plasma cells but could also emerge from various other factors affecting thrombopoiesis. These include issues at the progenitor level, reduced megakaryopoiesis, or increased platelet consumption or destruction in circulation.

Studies indicate that as MM progresses, there is a notable decrease in MK and platelet numbers even in the absence of treatment. Elevated levels of soluble P-selectin, IL-6, and TPO in MM patients correlate with disease severity, suggesting impaired thrombopoiesis at advanced stages (101).

Research by Kuang et al. demonstrated that newly diagnosed MM patients exhibited impaired megakaryopoiesis and thrombopoiesis, which worsened with disease progression. They identified metabolic factors, particularly increased serine secretion by MM cells into the bone marrow microenvironment, as a significant contributor to MK impairment via epigenetic modifications (5).

Thrombocytopenia-related bleeding in MM patients, though uncommon at presentation, can occur more commonly with IgA paraproteins, in the presence of high concentrations of serum immunoglobulins and high serum viscosity, conditions which all affect platelet function (6, 7, 102, 103). Studies have shown a reverse correlation between platelet counts and IgG2b levels in MM patients, indicating a potential role of paraproteins in thrombopoiesis impairment (5).

Qualitative changes in platelet function, such as reduced adhesion and aggregation responses, are also observed in MM. These changes have been attributed to direct interactions between paraproteins and platelet receptors such as GPIb (von Willebrand Factor receptor) or GPVI (collagen receptor) (104), an increased concentration of malondialdehyde (a marker of oxidative stress) (105), or the effect of a highly negatively charged λ dimer (106). These results indicate that impaired platelet function mostly due to the impact of paraproteins may underlie bleeding episodes reported in some MM patients.

Moreover, studies suggest a shortened lifespan of MM platelets compared to healthy controls, potentially due to abnormal platelet function or heightened intravascular activation (107, 108), which could contribute to impaired primary hemostasis in MM.

Overall, the above findings underscore the multifactorial nature of thrombopoiesis impairment in MM, involving both external factors from MM cells and bone marrow stroma (cytokines and EVs) affecting MKs and progenitors, and intrinsic abnormalities that may contribute to isolated thrombocytopenia.

Impaired secondary hemostasis: hypercoagulability and bleeding diatheses

While drug therapy-related thrombosis has been discussed earlier, hypercoagulability remains a significant complication of MM itself. Studies have indicated a heightened risk of VTE in MM and monoclonal gammopathy of undetermined significance (MGUS) patients, with a hazard ratio of 3.7 and 3.4 within the first year of diagnosis, respectively (109).

Hyperactivation of platelets emerges as a critical factor contributing to this risk. Increased levels of soluble P-selectin (101) or exposure of cell surface PS (54), two indicators of platelet activation, have been reported in newly diagnosed MM. O'Sullivan et al. demonstrated that platelet hyperactivation was prevalent not only in MM but also in the precursor stages of smoldering myeloma (SM) and MGUS, suggesting a continuum of platelet dysregulation from early stages of plasma cell neoplasia (110). In another study, they also reported that platelet hyperactivation identified at diagnosis would persist during treatments (111, 112). These studies imply that platelet hyperactivation as a prothrombotic factor exists in the precursor stages of MM, however, what drives this hyperactivation with the initiation phase of plasma cell neoplasia is unclear.

Abnormalities in secondary hemostasis in untreated MM are also documented. The ROADMAP-MM-CAT study identified procoagulant phospholipid clotting time (Procoag-PPL) and endogenous thrombin potential (ETP) as independent risk factors for VTE in MM. MM patients exhibited shortened Procoag-PPL clotting times but attenuated thrombin generation in platelet-poor plasma, accompanied by elevated levels of activated tissue factor, activated factor VII, and tissue factor pathway inhibitor, all posing the risk of thrombosis (113). In another study, MM patients presented a disbalanced thrombin generation profile characterized by an increased ETP but, at the same time, prolonged lag time and time-to-peak (TTP) in whole blood thrombin generation. RBCs and platelets in whole blood were suggested as the source of this disbalanced hemostasis posing the risks of both thrombophilia and bleeding in MM patients (114).

Elevated levels of coagulation proteins including FVIII and von Willebrand factor (vWF) are reported in MM, associated with an

increased risk of thrombotic complications, particularly in advanced disease stages (115). Indeed, a strong association of high FVIII and vWF levels with thrombosis risk in general has been documented (116). The mechanism behind this elevation is likely multifactorial, potentially involving endothelial cell activation induced by MM cells or bone marrow MSCs, which secrete angiogenic cytokines such as vascular endothelial growth factor (VEGF) (117).

Rare cases of bleeding diatheses due to coagulopathy, such as acquired von Willebrand syndrome (AvWS) (118, 119), acquired factor IX deficiency (120), and acquired factor X deficiency (121, 122), have also been documented in MM. In all these cases, it has been suggested that paraproteins can interact with the coagulation protein impairing its function and resulting in bleeding symptoms. Of note, amyloid proteins may also underlie acquired factor X deficiency as some patients with amyloid light-chain (AL) amyloidosis develop concomitant factor X deficiency (123).

In summary, MM-related hypercoagulability and bleeding diatheses are complex phenomena involving dysregulation of platelets, abnormalities in coagulation factors, and interactions between paraproteins and hemostatic proteins. These factors collectively contribute to the thrombotic and bleeding risks observed in MM patients.

Clinical recommendations

Thrombocytopenia may develop in MM following treatment with novel agents including VRD (lenalidomide-bortezomib-dexamethasone), carfilzomib, or a combination of the four drugs (124). Autologous stem cell transplantation (ASCT) preceded by a myeloablative high-dose therapy (HDT) such as melphalan and followed by a maintenance protocol including IMiDs or PIs remains the standard of care for newly diagnosed MM patients per evidence-based recommendations (level of evidence I, mSMART 2019) (125), but thrombocytopenia continues to be one of the major adverse events in this approach. According to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, thrombocytopenia of 25-50 × 10^3/μL is defined as grade 3, and <25 × 10^3/μL as grade 4. Meta-analysis of the effectiveness of PIs (126) and IMiDs (127) in the analyzed randomized controlled trials (RTCs) identified grades 3-4 thrombocytopenia in MM patients. Kroger's study using BU (busulfan) and CY (cyclophosphamide) as the conditioning regimen for allogeneic stem cell transplantation (allo-SCT) and lenalidomide for maintenance in refractory/relapsed MM, reported grade 3-4 thrombocytopenia in 16% of patients. Furthermore, a phase IIb, multicenter, open-label study of high-dose melphalan (in a propylene glycol-free formulation) for myeloablative conditioning in MM patients undergoing ASCT reported only grade 4 thrombocytopenia in 98% of the patients (60/61) (128).

Thrombocytopenia of grades 3 or 4 may culminate in life-threatening hemorrhage if not managed properly and in a timely manner. If platelet transfusion is decided, it should follow established guidelines, such as those provided by the American Society of Clinical Oncologists (level of evidence II) (129). Although it is recommended that invasive procedures be minimized in MM patients with thrombocytopenia, a platelet count of 40 × 10^3/μL to 50 × 10^3/μL is considered safe for proceeding with invasive procedures provided that the patient does not present any other coagulation abnormalities (129). The consensus statement of the International Myeloma Foundation (IMF) Nurse Leadership Board also recommends that MM patients with thrombocytopenia avoid taking drugs that impair PLT function such as aspirin, ibuprofen, or naproxen unless otherwise instructed (e.g., for prophylaxis of thromboembolic events); avoid activities that can result in bleeding or bruising such as contact sports or tattooing; and use soft sponges and non-abrasive toothpaste for their oral care (130).

Thrombotic events related to drugs such as IMiDs also require robust clinical management. A recent publication of the *Intergroupe Francophone du Mye'lome* (IFM) group recommends thromboprophylaxis using low molecular weight heparin (LMWH) or direct oral anticoagulants (DOACs) in MM patients who receive IMiDs combined with dexamethasone (131). However, the dose of LMWH or DOACs needs to be adjusted depending on renal function using the creatine clearance (CrCl) test. If CrCl is >30mL/min, no adjustment is required but if it is below 15mL/min, none of these anti-coagulants should be used and the patient must receive unfractionated heparin (UFH) instead (131). Following the International Myeloma Working Group (IMWG) guidelines, the choice of prophylactic treatment should be made on the basis of risk factors including those related to therapy, individual (patient), and active myeloma *per se* among others (132). They recommend prophylactic dose LMWH or full-dose warfarin (target INR 2-3) for MM patients who have at least one therapy-related or at least two patient- or myeloma-specific risk factors, and aspirin for other patients who may be at lower risk. DOACs such as apixaban and rivaroxaban, the new generation of oral anticoagulants, were not included in the IMWG guidelines. Although most phase III RCTs employing DOACs did not include MM patients, small studies have shown their promising effectiveness as substitutes to LMWH and warfarin which are inconvenient due to parenteral route and need for INR monitoring, respectively (133, 134).

Other than thrombotic events related to IMiDs, targeted therapy-associated cardiovascular adverse events have also been reported in MM following treatments with monoclonal antibodies and PIs. Two separate disproportionality analyses on reports from the FDA Adverse Event Reporting System (FAERS) database identified daratumumab, elotuzumab, isatuximab, and panobinostat to be mostly associated with cardiotoxicity (135, 136). Another study using the same database reported a significant disproportional association between carfilzomib and cardiovascular events in MM patients (137). Although further prospective studies are required, the above reports highlight the importance of closely monitoring MM patients under these treatments, particularly if they present with a cardiac history.

Finally, impaired function of PLTs or coagulation factors unrelated to therapy could also contribute to bleeding risk in MM patients. Thus, comprehensive hemostatic assessments for newly

diagnosed or untreated MM patients are crucial to identify underlying primary or secondary hemostasis abnormalities. These assessments should include coagulation factor assays, intrinsic coagulation inhibitor assays, or platelet function studies, particularly aggregometry. Early identification and management of these disorders can improve clinical outcomes and reduce the risk of further complications during treatment.

Future directions

In the realm of research, several gaps remain in our understanding of how MM impacts coagulation factors during its oncogenic process, how it impairs platelet function, and crucially, the molecular mechanisms driving MSC-mediated impaired thrombopoiesis. Investigating thrombopoiesis in *in vitro* settings using co-culture models of MM cells with HSCs, especially in the presence of MSCs from MM patients' bone marrow, could help elucidate the cellular and molecular mechanisms underlying acquired hemostatic abnormalities in MM. Addressing these gaps will not only advance our understanding of MM-associated hemostatic disorders but also pave the way for developing more effective therapies tailored to these specific pathophysiological mechanisms. Future research should focus on targeted therapies that modulate the bone marrow microenvironment and improve platelet production and function in MM patients. This could include exploring the therapeutic potential of MSCs and exosomes and the development of novel drugs that target specific pathways involved in thrombopoiesis and coagulation.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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