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Review article

Rediscovering hemostasis abnormalities in multiple myeloma: The new era

Yudie Huang [a,b,1], Chongyu Wang [b,1], Hua Wang [c,**], Hong Liu [a,***], Lu Zhou [a,b,d,*]

[a] Department of Hematology, Affiliated Hospital of Nantong University, Jiangsu, 226001, China
[b] Nantong University, Jiangsu, 226001, China
[c] Department of Pediatrics, Loma Linda University School of Medicine, CA, 92350, USA
[d] NHC Key Laboratory of Thrombosis and Hemostasis, The First Affiliated Hospital of Soochow University, Soochow, 215000, China

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ABSTRACT

Multiple myeloma (MM) is a malignancy arisen from the abnormal proliferation of clonal plasma cells. It has a high risk of developing bleeding and thrombotic complications, which are related to poor prognosis and decreased survival. Multiple factors are involved in the breaking of the hemostasis balance, including disease specific factors, patient-specific factors, and drug factors that change pro-and anticoagulant and fibrinolysis. Recently, with the introduction of new treatments such as monoclonal antibodies, chimeric antigen receptor modified T-cell therapy, antibody-drug conjugates directed against BCMA, programmed death-1 inhibitor, export protein 1 inhibitors, histone deacetylase inhibitors, immunomodulatory drugs, proteasome inhibitors and Bcl-2 inhibitors, the therapy of MM patients has entered into a new era. Furthermore, it arouses a question whether these new treatments would alter the hemostasis balance in MM patients, which highlights the importance of the underlying pathophysiology of hemostasis abnormalities in MM, and on prophylaxis approaches. In this review, we updated the mechanisms of hemostasis abnormalities in MM, the impact of the new drugs on hemostasis balance and reliable therapeutic strategies.

1. Introduction

Multiple myeloma (MM) is a plasma cell disease characterized by clonal proliferation of bone marrow plasma cells and excessive production of monoclonal immunoglobulin [1]. It is one of the most common malignancies in hematopoietic system, accounting for about 10 % of.hematological malignancies [2]. It is a senile disease [3]. Approximately 160,000 new patients are diagnosed each year, and this number is steadily rising with an increased aging population [4].

MM patients frequently experience bleeding and thromboembolism that seriously threaten their life [5,6]. Reports show that they had hazard ratios of 7.5 for venous thromboembolism (VTE) and 1.7 for arterial thromboembolism (ATE) compared with their matched controls [7,8]. And in one study, more than half of MM patients had bleeding complications (52.4 %) [9]. Multiple factors are

* Corresponding author. Hematology Department, Affiliated Hospital of Nantong University, 20 Xisi Road, Nantong, Jiangsu, 226001, China.
** Corresponding author.
*** Corresponding author. Hematology Department, Affiliated Hospital of Nantong University, 20 Xisi Road, Nantong, Jiangsu, 226001, China.
E-mail addresses: hongliu63@126.com (H. Liu), xueyezhoulu2007@sina.com (L. Zhou).
[1] These authors have contributed equally to this work and share the first authorship.

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involved in the breaking of the hemostasis balance, including disease specific factors, patient-specific factors, and drug factors that change pro-and anticoagulant and fibrinolysis (Fig. 1) [5,6]. Hemorrhage and thromboembolism can result in impaired quality of life, treatment delay or discontinuation, and decreased overall survival rate in MM patients [6,10].

Recent years, the advent of new therapies, including monoclonal antibodies, chimeric antigen receptor modified T-cell therapy, antibody-drug conjugates directed against BCMA, programmed death-1 inhibitor, export protein 1 inhibitors, histone deacetylase inhibitors, immunomodulatory drugs, proteasome inhibitors and Bcl-2 inhibitors, has raised the issue of whether novel therapies could induce abnormal coagulation, causing unwanted bleeding or thromboembolism, and what management could be done to prevent this problem [11]. In this review, we updated the mechanisms of hemostasis abnormalities in MM, the impact of the new drug on coagulation abnormalities and reliable therapeutic strategies.

1.1. Mechanisms of bleeding complications in MM

Bleeding in MM patients generally occurs in the early stage of the disease [12]. It usually manifests as mucocutaneous bleeding (typically periorbital purpura, epistaxis, menorrhagia), sometimes as severe abdominal or gastrointestinal bleeding [13,14]. Bleeding from the lungs (e.g., pulmonary hemorrhagic nephritis syndrome) [15] or intracranial hemorrhage are rare [13]. Hyperviscosity, reduced platelet count and dysfunction, and abnormalities in the coagulation and fibrinolysis system are all involved in the mechanism of bleeding in MM patients [13,16].

1.2. Hyperviscosity

Excessive production of abnormal clonal gamma globulin or paraprotein leads to increased blood viscosity, resulting in hyperviscosity syndrome, which not only causes thrombotic complications but also bleeding complications due to elevated circulating proteins that impact platelet aggregation [17,18]. Hyperviscosity is related to the number of M proteins as well as the type of M proteins, IgM has the capability to form large cyclic pentamers of high molecular weight, resulting in high viscosity [13,19]. IgA also has the ability to polymerize or form aggregates [19]. IgG is rarely involved due to its low molecular weight and requires high serum

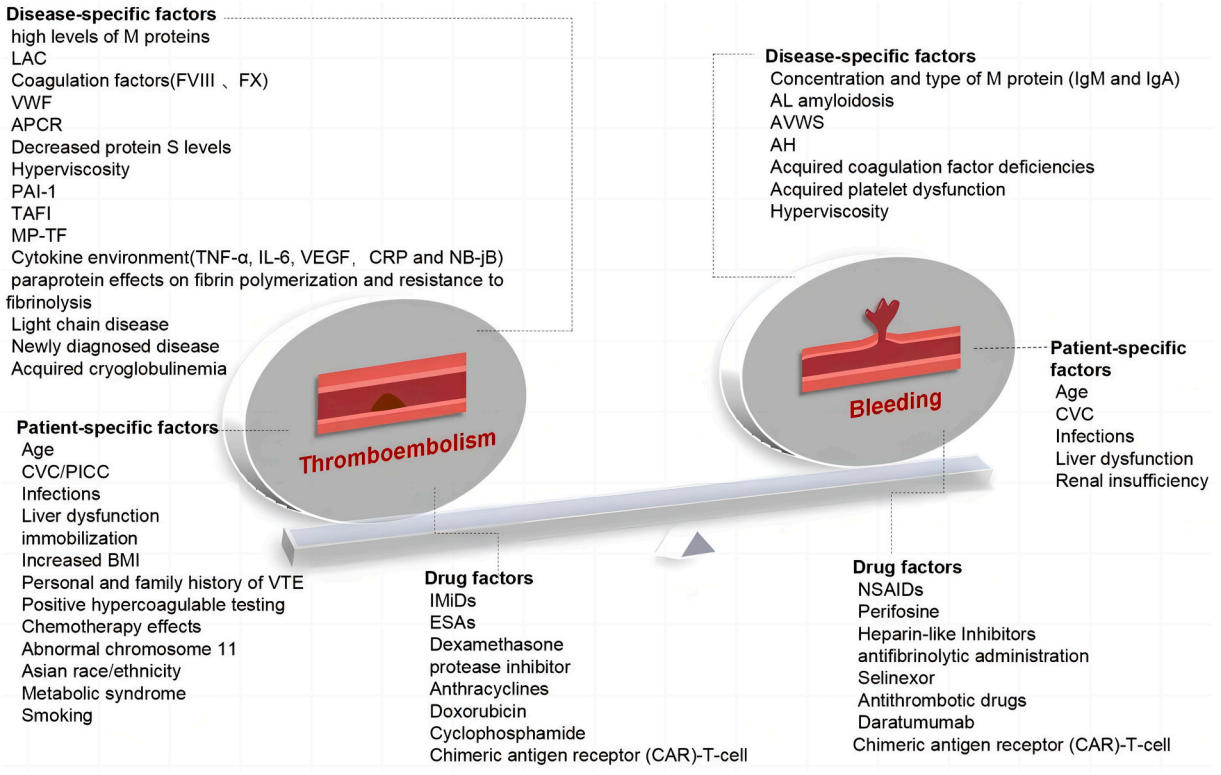

Fig. 1. Risk factors for bleeding and thrombosis in multiple myeloma patients. Abbreviations: LAC, lupus anticoagulant; APCR, activated protein C resistance; PAI-1, plasminogen activator inhibitor; FVIII factor VIII, FX: factor X, VWF: von Willenbrand factor; TAFI, thrombin activatable fibrinolysis inhibitor; MP-TF, tissue factor microparticle; TNF-α, tumor necrosis factor-α; IL-6, Interleukin- 6; VEGF, vascular endothelial growth factor; CRP, C-reactive protein; CVC, central venous catheters; PICC, Peripherally Inserted Central Catheter; BMI, body mass index; VTE, venous thromboembolism; AL amyloidosis, light-chain amyloidosis; AVWS, acquired von Willebrand syndrome; AH, acquired hemophilia; IMiDs, immunomodulatory drugs; NSAIDs, nonsteroidal anti-inflammatory drugs; ESAs, erythropoietic stimulating agents.

concentrations or the formation of monoclonal IgG aggregates in order to impact plasma viscosity [19]. However, IgG3 is an exception as it can form unstable complexes at moderate concentrations [19].

1.3. Reduced platelet count and dysfunction

Thrombocytopenia is very common and is thought to be a poor prognostic factor affecting survival in patients with MM [20]. It is usually caused by multiple factors, including the harmful impact of chemotherapy drugs on megakaryocytes, the inhibition of regular hematopoiesis by cancerous cells, and the replacement of bone marrow tissue by myeloma cells [21,22]. And a recent study showed that MM cells produce and release a large amount of serine into the bone marrow microenvironment, which is uptake by SLC38A1 (a transporter), and inhibit the expression of SVIL (an actin-binding protein related to cytokinesis) via S-adenosyl-methionine (SAM), ultimately leading to the disorder of megakaryocyte production and the inhibition of platelet production [20]. Moreover, this study also showed that the effect of serine on thrombocytopenia can also be mediated by inducing platelet apoptosis in peripheral blood [20]. In addition, dysfunction in platelet aggregation and adhesion is also related to bleeding tendency [23]. It showed that paraproteins produced by monoclonal plasma cells could bind specifically to platelet antigens (GPIb, GPIIIa or GPVI) and the A1 domain of VWF (Von Willenbrand Factor), hindering platelet adhesion and aggregation [23].

1.4. Abnormalities in the coagulation and fibrinolysis systems

Acquired coagulation factor deficiency is another reason for bleeding in MM [24,25]. Several mechanisms were reported to be responsible for acquired coagulation deficiency in MM patients, including the formation of a complex between paraprotein and FX, which is subsequently sequestered by the reticuloendothelial system, IgG4-mediated specific FX inhibitor blocks the activation of FX, and absorption of FX by amyloid fibres in patients concomitant with amyloidosis [25].

MM patients may also have acquired dysfibrinogenemia, which is caused by the inhibition of fibrin formation by paraproteins [26]. The underlying mechanisms include: (1) the high level of paraproteins in plasma induces an increase in plasma viscosity to alter fibrin polymerization; (2) paraproteins can be used as anti-fibrinogen antibodies to bind to fibrinogen, and (3) paraproteins may bind to fibrinogen through non-specific reactions [26–28]. Interestingly, paraproteins do not affect the interaction between thrombin and fibrinogen and the release of fibrin peptide, but they interact with fibrinogen γ chain, changing the formation and network structure of fibrils, reducing the mass to length ratio of fibrin fibers and increasing the hardness of fibrin gel [27,28]. They also reduce the lateral gathered to form gelatinous fragile clots, resulting in bleeding [27,28].

1.5. Mechanisms of thrombosis in MM

Patients with MM are at a higher risk of thromboembolism than bleeding, which is a common cause of death for MM [6]. Thrombosis mainly includes VTE and ATE. VTE includes deep vein thrombosis (DVT), pulmonary embolism, central venous catheter-related thrombosis, and arm vein thrombosis [29]. ATE includes ischemic stroke, transient ischemic attack (TIA), and myocardial infarction [30]. A study reported the amplified risks for VTE and ATE following 1-, 5-, and 10-year follow-ups. The risks were increased 7.5-, 4.6-, and 4.1-fold for VTE and 1.9-, 1.5-, and 1.5-fold for ATE, respectively [8,30]. Studies have shown that somatic tumor mutations in STK11, KRAS, CTNNB1, KEAP1, CDKN2B and MET are associated with increased VTE risk [31], and cancers somatic genetic changes in KRAS and STK11 are associated with increased ATE risk [6,32]. However, these genomic alterations were not identified in MM patients [6]. The mechanism of thrombosis in MM patients may be caused by the inflammatory environment, abnormal metabolic environment and abnormal coagulation and fibrinolysis system [13,33,34].

1.6. Inflammatory environment

Inflammation is closely related to the occurrence of thrombosis [35,36]. MM patients express high levels of inflammatory factors such as interleukin-6 (IL-6), transforming growth factor-β (TGF-β), C-reactive protein (CRP), and tumor necrosis factor (TNF), contributing to the occurrence of thrombosis [16,37]. Among them, IL-6 plays a key role in the coagulation process. On one hand, IL-6 promotes coagulation by promoting the FVIII gene transcription [16] and enhances fibrinogen production by binding to CTGGGA hexanucleotide clusters in the promoter regions of fibrinogen alpha and gamma chain genes [13,38,39]. On the other hand, it reduces the activity of plasminogen activator inhibitor 1 (PAI-1), leading to low fibrinolysis [13,40]. In addition, it also stimulates liver cells and other cells to release CRP that indirectly mediates increased expression of tissue factor (TF) [16,41]. TF is an important initiating factor in the exogenous coagulation pathway. It increased the expression of TNF-α and NB-jB, which promotes TF expression through negative feedback mechanism, leading to thrombosis [42,43]. After blocking NB-jB in a mouse model, TF expression was reduced, and the incidence of DVT was reduced [42]. The inflammatory and profibrotic effects of TGF-β are associated with thrombosis [44]. TGF-β1 signaling through TGF-β receptor I promotes fibrosis and endothelial dysfunction, thereby impairing thrombus resolution [45].

1.7. Coagulation and fibrinolysis system

The increase of FVIII and VWF is related to thrombosis [46]. Study showed a significant increase in the number and activity of VWF antigen (VWF: Ag) and FVIII activity (FVIII:C) in newly-diagnosed MM patients [46]. During the treatment of immunomodulatory drugs (IMiDs), there is also an increase in VWF and FVIII [47]. Dysregulation of the VWF/ADAMTS-13 axis, increasing of bone marrow

Table 1
Coagulation-related adverse events and clinical response to MM patients with new-generation drugs.

Clinical trial	Patient	N =	Treatments	Clinical response	Hemostasis abnormalities	Ref
NCT03548207	RRMM	97	Ciltacabtagene autoleucel	sCR 82.5 % CR 0 % VGPR 12.4 % PR 3.1 %	Thrombocytopenia 79.4 %, grade 3/4 59.8 %	[68]
NCT03361748	RRMM	128	Idecabtagene vicleucel	sCR/CR 33 % VGPR 52 %	Thrombocytopenia 63 %, grade 3/4 52 % Bleeding grade 3/4: 4 events	[69]
NCT02064387 (Part 2)	RRMM	35	Belantamab mafodotin	sCR 3 % CR 6 % VGPR 43 % PR 9 %	Thrombocytopenia 57 %, grade 3/4 34 %	[70]
NCT03525678	RRMM	196	Belantamab mafodotin (2.5 mg/kg n = 97, 3.4 mg/kg n = 99)	≥VGPR 19 % vs 23 % ≥PR 58 % vs 66 %	Thrombocytopenia grade3/4 20 % vs 33 %	[71]
NCT02579863	NDMM	301	Pembrolizumab + lenalidomide + DEX VS lenalidomide + DEX	sCR 2.0 % vs 1.3 % CR 1.3 % vs 2.0 % VGPR 21.9 % vs 18.7 % PR 38.4 % vs 40.0 %	ITP 0.07 % vs 0 %, PE 1.3 % vs 0.7 %	[72]
NCT03848845	RRNN	41	Belantamab mafodotin + pembrolizumab	Parts 1 and 2 sCR 0 % CR 4 % VGPR 6 % PR 6 %	Thrombocytopenia 35 %, grade ≥3 29 %	[73]
NCT03944057	RRMM	82	Selinexor and DEX	VGPR 4.9 % PR 24.4 %	Thrombocytopenia 87.8 %, grade 3/4 51.2 %	[74]
NCT01607892	RRMM	84	Selinexor alone Selinexor 45 mg/m^2 + DEX 20 mg Selinexor 60 mg/m^2 + DEX 20 mg	CR 1 %/PR 8 %	Thrombocytopenia 52 %, grade 3/4 45 %	[75]
NCT02199665	RRMM	21	Selinexor plus CFZ and DEX	CR 0 % VGPR 14 % PR 33 %	Thrombocytopenia 81 %, grade 3/4 71 % Bleeding: n = 1 (unrelated to treatment) DVT and PE: n = 1	[76]
NCT02477891	RRMM	293	Daratumumab	sCR 0.3 % CR 2.4 % VGPR 9.6 % PR 20.8 %	Thrombocytopenia grade3/4 18.8 %	[77]
NCT02852837	RRMM	50	Daratumumab	sCR 2.1 % CR 6.4 % VGPR 19.1 % PR 14.9 %	Thrombocytopenia 31.9 %, grade 3/4 19.1 %	[78]
NCT02519452	RRMM	53	Daratumumab and rHuPH20 (DARA 1200 mg n = 8, DARA 1800 mg n = 45)	1200 mg: ORR 25 % 1800 mg: sCR 8.9 % VGPR 11.1 % PR 22.2 %	1200 mg: Thrombocytopenia 37.5 %, grade 3/4 12.5 % 1800 mg: Thrombocytopenia 17.8 %, grade 3/4 6.7 %	[79]
NCT01496118	RRMM	33	Panobinostat and CFZ	CR 6.3 % VGPR and nCR 34.4 % PR 43.8 %	Thrombocytopenia 78.8 %, grade ≥3 60.6 %	[80]
NCT02290431	RRMM	31	Panobinostat plus DEX and bortezomib	CR 25.8 % VGPR 22.6 % PR 32.3 %	Thrombocytopenia 54.8 %, grade 3/4 48.4 %	[81]
NCT01311687	RRMM	455	Pomalidomide plus low-dose dexamethasone VS high-dose dexamethasone	CR or sCR 1 % vs 0 % VGPR 5 % vs < 1 % PR 26 % vs 9 %	Thrombocytopenia 30 % vs 29 % grade 3 9 % vs 9 % grade 4 13 % vs 17 %	[82]
NCT01351623	RRMM	44	Carfilzomib	CR 2 % VGPR 21 % PR 31 %	Thrombocytopenia grade3/4 32 %	[83]

(*continued on next page*)

Table 1 (*continued*)

Clinical trial	Patient	N =	Treatments	Clinical response	Hemostasis abnormalities	Ref
NCT01794507	RRMM	66	Venetoclax + bortezomib and DEX	sCR 5 % CR 15 % VGPR 23 % PR 24 %	Thrombocytopenia 39 %, grade 3/4 29 %	[84]
NCT01794520	RRMM	66	Venetoclax	sCR 3 % CR 4 % VGPR 8 % PR 6 %	Thrombocytopenia 21 %, grade 3/4 17 %	[85]

Ref, Reference; RRMM, relapsed/refractory multiple myeloma; NDMM, newly diagnosed multiple myeloma; ITP, immune thrombocytopenia; PE, pulmonary embolism; Vd, bortezomib-dexamethasone; CFZ, carfilzomib; DEX, dexamethasone; ORR, overall response rate; CR, complete response; sCR, stringent complete response; nCR, near complete response; PR, partial response; VGPR, very good partial response; DVT, deep vein thrombosis.

angiogenesis, and chronic activation and dysfunction of endothelial may be responsible for the increase [46]. Prolonged VWF half-life was also found, indicating reduced circulating clearance of VWF [48]. It is possible that abnormally glycosylated VWF is present in MM due to the high level of sialylation. However, VWF clearance is a complex process, and the analysis of VWF clearance has not been evaluated [48].

The structure and function of plasma fibrin clots are defected in all types of myeloma patients, including slower clot formation and reduced lytic capacity [49]. This may be related to the fact that immunoglobulin competes with coagulation FXIII to bind to the lateral binding site of plasmin, and FXIII cannot act on fibrin, resulting in the inability of blood clots to shrink [16]. Another reason is the significant increase in thrombin generation (TG) potential in MM [49]. As a result, coagulant properties of fibrinogen and other proteins that contribute to fibrin synthesis and/or degradation are altered, leading to denser clots composed of fine fibers [49,50]. And the increase level of thrombin potentially activates thrombin activatable fibrinolysis inhibitor (TAFI), leading to the increase of TAFI activity and the decrease of fibrinolytic ability [49,50].

MM patients exhibit activated protein C (APC) resistance and acquired protein S (PS) abnormalities in the absence of factor V Leiden mutation [51]. Protein C is an important anticoagulant in the body. APC inactivates FVa and FVIIIa with the help of PS, which leads to a decrease in thrombin production [52]. APC resistance disrupts anticoagulant activity, compounded by the abnormal function of PS, thus leading to a hypercoagulable state [51]. Several factors, such as M protein levels, active disease state, and CRP have been implicated in promoting APC resistance in MM patients [46]. However, their specific roles in modulating APC's anticoagulant activity remain to be fully elucidated [46].

1.8. Metabolic syndrome

Metabolic syndrome (MS) increases the risk of ATE in MM patients, leading to cardiovascular diseases such as atherosclerosis, myocardial infarction, and stroke [53]. It includes obesity (central obesity), hyperglycemia, insulin resistance, hypertension and dyslipidemia [54,55]. Dyslipidemia, which includes hypercholesterolaemia, hypertriglyceridaemia, and low high-density lipoprotein cholesterol, is common in patients with the IgA subtype [56–58].

It has been found that obesity increases mortality and is a risk factor for the development of MM [57]. Obesity is no longer a disease caused by simple lipid accumulation but rather a chronic inflammatory disease related to adipocyte dysfunction and the endocrine activity of adipose tissue (AT) [33]. Several researchers have shown that inflammation of AT increases the production of CRP and fibrinogen in the liver. As a result, adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) are stimulated, leads to the formation of a prothrombotic state that eventually develops into cardiovascular disease [34,59,60]. Both MM and obesity can lead to the elevation of IL-6 and TNF-α, which play an important role in thrombosis [16,33]. IL-6 and TNF-α promote the synthesis of TF, which can mediate exogenous coagulation [61]. IL-6 promotes the release and activation of thrombin by reducing the production of the anti-coagulatory factor anti-thrombin [62]. Moreover, injection of IL-6 into the body can increase the number of platelets [63]. TNF-α not only induces the expression of adhesion molecules on endothelial cells but also stimulates platelet aggregation and induces leptin and PAI-1 synthesis in AT [64].

Diabetes mellitus (DM) is also a cause of increased MM development and mortality [65]. The exact mechanism between DM and VTE is unclear, but a case of DVT in IgGκ MM patients with diabetes have been reported [66]. The possible mechanism is that hyperglycemia and insulin resistance promote the increased production of PAI-1, whose function is mainly to block t-PA, resulting in reduced its activity and a prothrombotic state [66].

1.9. Effects of new generation drugs on hemostasis balance

Treatment can also increase the risk of bleeding and thrombosis in patients with MM [7,67]. For instance, anthracycline drugs can enhance the transferrin activity of vascular endothelial cells, which leads to the decrease of the ability of endothelial cells to activate PC [13]; Doxorubicin induces a procoagulant phenotype in endothelial and monocytes, leading to increased plasma thrombin production [67]. In recent years, the treatment of MM has more options, and the toxic effects of new drugs are of concern (Table 1). Moreover, many clinical trials on new drugs are under way (Table 2).

1.10. CAR-T therapy

Chimeric antigen receptor T (CAR-T) cell therapy has brought revolutionary changes to the treatment of relapsed/refractory multiple myeloma (RRMM) [86]. Although it had improved the PFS and OS of MM patients, its' specific toxicities, such as cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) and hemostasis complications, are key challenges to CAR-T therapy [87,88]. Regarding the toxicity of CAR-T therapy, the CAR-HEMATOTOX (HT) score was developed [89]. Laboratory markers were granted a maximum leniency period of three days [89]. One point was designated for these conditions: absolute neutrophil count $\leq$1200/μl, hemoglobin $\leq$9.0 g/dl, platelet count 76–175 G/l, CRP $\geq$3.0 mg/dl, and ferritin levels between 650 and 2000 ng/ml [89]. Two points were set for a platelet count of 75 G/l or less and ferritin levels of 2000 ng/ml or more [89]. Scores exceeding 2 were categorized as high risk (HT^{high}), while scores between 0 and 1 were deemed low risk (HT^{low}) [89]. This scoring system can be used for pre-treatment risk assessment, aiding in risk management and tailoring interventions for CAR-T-related toxicity [89].

Thrombocytopenia is one of the common toxic effects of CAR-T therapy [68,69]. A clinical trial involving 128 patients showed that 127 patients experienced grade 3/4 hematologic adverse events, 67 (52 %) of which were thrombocytopenia [69], which is an important factor for predicting the risk of bleeding [86]. The development of thrombocytopenia following anti-BCMA CAR-T therapy for MM has been documented [90]. The mechanism of thrombocytopenia post-CAR-T treatment is still not well understood [90]. However, the rise in IL-6 and IL-10 levels following CAR-T cell infusion could mirror the patients' immune condition: elevated IL-6 disrupts the equilibrium of Treg/Th17 cells and triggers CD8 T cells and antibody generation, while elevated IL-10 stimulates immune responses and enhances cytotoxic activity, leading to immune-mediated destruction of platelets [90]. Bleeding was also observed in patients with high-grade ICANS, possibly due to severe fibrinogen depletion [86].

Previously, our group described a case of a relapsed and refractory multiple myeloma (RRMM) patient who exhibited severe femoral vein thrombosis, thrombocytopenia, hemorrhagic tendencies, and severe CRS following CAR-T treatment [88]. Thrombosis may be associated with multiple cytokines, such as IL-1, IL-6, IL-10, IFN-γ, and TNF-α, are released from CRS which is a systemic inflammatory response [88,91]. In addition, the increased risk of thrombosis may be due to endothelial cell activation and vascular injury [91].

Table 2
Ongoing clinical trial.

Clinical trial	Official Title [ICMJE]	Status
NCT04727008	Phase I Study of A CXCR4 Modified BCMA CAR-T in Patients With Refractory and/or Relapsed Multiple Myeloma	Recruiting
NCT04318327	Phase I, Open Label, Study of B-cell Maturation Antigen (BCMA)-Directed CAR-T Cells in Adult Patients With Multiple Myeloma	Active, not recruiting
NCT04795882	An Open Label, Phase 1 Study Evaluating the Activity of Modular CAR T for myeloma	Enrolling by invitation
NCT05204160	Phase II Study of Pembrolizumab as Salvage Therapy Among Multiple Myeloma Patients Progressing on CAR-T Cell Therapy	Recruiting
NCT04398745	A Phase I Study to Evaluate the Pharmacokinetics and Safety of Belantamab Mafodotin Monotherapy in Participants With Relapsed and/or Refractory Multiple Myeloma (RRMM) Who Have Normal and Varying Degrees of Impaired Renal Function (DREAMM 12)	Recruiting
NCT04398680	A Phase I Study to Evaluate the Pharmacokinetics and Safety of Belantamab Mafodotin Monotherapy in Participants With Relapsed or Refractory Multiple Myeloma Who Have Normal and Varying Degrees of Impaired Hepatic Function (DREAMM 13)	Recruiting
NCT05514990	A Phase 1b/2 Study of Standard Doses of Bortezomib and Pembrolizumab ± Reovirus (Pelareorep) Combination Therapy in Patients With Relapsed Multiple Myeloma (AMBUSH Study)	Recruiting
NCT04782687	Phase II Trial of Daratumumab, Lenalidomide and Dexamethasone (DRd) in Combination With Selinexor for Patients With Newly Diagnosed Multiple Myeloma	Recruiting
NCT06212596	A Randomised Phase II Trial of Selinexor, Cyclophosphamide and Prednisone vs Cyclophosphamide and Prednisone in Relapsed or Refractory Multiple Myeloma (RRMM) Patients	Completed
NCT02343042	A Phase 1b/2 Study of Selinexor (KPT-330) in Combination With Backbone Treatments for Relapsed/Refractory Multiple Myeloma and Newly Diagnosed Multiple Myeloma	Active, not recruiting
NCT05139225	A Phase Ib Study Of The Combination Of CD47 Blockade With SIRP-Alpha FC Fusion Proteins (TTI-622) And Daratumumab Hyaluronidase-fihj For Patients With Relapsed or Refractory Multiple Myeloma	Recruiting
NCT04151667	Phase II Study of Daratumumab Based Response Adapted Therapy for Older Adults With Newly Diagnosed Multiple Myeloma	Active, not recruiting
NCT06107738	IBEX: Phase 2 Trial of Iberdomide + SQ Daratumumab as Post-Autologous Stem Cell Transplant Maintenance Therapy in Multiple Myeloma	Recruiting
NCT02506959	Panobinostat Combined With High-Dose Gemcitabine/Busulfan/Melphalan With Autologous Stem Cell Transplant for Patients With Refractory/Relapsed Myeloma	Active, not recruiting
NCT02506959	Panobinostat Combined With High-Dose Gemcitabine/Busulfan/Melphalan With Autologous Stem Cell Transplant for Patients With Refractory/Relapsed Myeloma	Active, not recruiting
NCT06115135	A Phase 2 Study of Venetoclax in Combination With Isatuximab and Dexamethasone for Relapsed/Refractory Multiple Myeloma Patients With t (11; 14)	Not yet recruiting
NCT02899052	A Phase 2, Open-Label, Multi-Center Study of Venetoclax in Combination With Carfilzomib and Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma	Active, not recruiting

2. Antibody-drug conjugates directed against BCMA

Belantamab mafodotin is an antibody-drug conjugate (ADC) targeting BCMA [92,93]. Its interaction with BCMA promotes monomethyl auristatin F internalization and release, activating caspase-3-dependent apoptosis [92,93]. In addition, after the release of antigens from MM cells following apoptosis, macrophages mediate cell death through antibody-dependent cellular phagocytosis. Moreover, antibody a fucosylation enhanced antibody-dependent cell-mediated cytotoxicity [92,93].

Belantamab mafodotin has shown promising efficacy in phase 1 and 2 single-agent studies [70,71]. Thrombocytopenia and keratopathy were the most common adverse events [70,71]. Thrombocytopenia is considered self-limited and can be controlled by modifying the treatment plan [94]. At present, there are no studies on the mechanism of thrombocytopenia caused by Belantamab mafodotin and no reports of thrombotic events, which need to be further studied.

2.1. Programmed death-1 inhibitor

Pembrolizumab, a programmed death-1 (PD-1) inhibitor, has shown promising clinical efficacy in some solid tumors and hematological malignancies, such as Hodgkin's lymphoma [95,96]. MM, like other tumors, has increased expression of PD-1 ligand (PD-L1) [95]. For RRMM patients, pembrolizumab shows as a potential treatment option [95]. It has so far been shown that in RRMM, monotherapy is ineffective, but combination therapy with IMiDs and dexamethasone also has promising results [97]. However, the safety of pembrolizumab needs to be further evaluated [96]. In the Keynote-185 study, one case of immune thrombocytopenia and two cases of pulmonary embolism occurred [72]. PD-1 inhibitors exert antitumor effects by reactivating exhausted T cells [98]. Reactivated T cells cause inflammation, which can lead to thrombosis [98]. Moreover, ongoing studies of pembrolizumab plus IMiDs and dexamethasone were suspended because of a higher incidence of adverse events and death among patients in the pembrolizumab group [95]. In other treatment strategies, pembrolizumab plus lenalidomide and dexamethasone as consolidation therapy after autologous stem cell transplantation and belantamab mafodotin plus pembrolizumab demonstrated favorable efficacy [99,73].

2.2. Export protein 1 inhibitor

Export protein 1 (XPO1) is a nuclear export protein that is overexpressed in MM cells and is crucial for their survival [100]. Selinexor is a selective inhibitor of nuclear export (SINE) compound that treats RRMM by specifically inhibiting XPO1 [100]. However, the therapeutic application of selinexor can induce severe thrombocytopenia [74–76]. This side effect may arise from abnormal pSTAT3 accumulation in the megakaryocyte nucleus and the subsequent upregulation of its downstream target, Klf4, in the thrombopoietin (TPO) signaling pathway, eventually leading to Oct4 induction [100,101]. Increased Klf4 and Oct4 may maintain stem cells in an undifferentiated state, thereby preventing the differentiation and maturation of megakaryocytes [101]. Selinexor has no direct cytotoxic impact on platelets or megakaryocytes [101,102]. In vitro and in vivo studies have demonstrated that selinexor-induced thrombocytopenia is reversible, thus supporting the temporary cessation of drug administration [101]. When platelet counts are low, thrombopoietin receptor agonists (e.g., eltrombopag) or transfusions are necessary [102].

2.3. Monoclonal antibody against CD38

Daratumumab (DARA) is a monoclonal antibody against CD38 [103]. As a new drug for the treatment of MM, DARA has shown significant clinical efficacy [103]. The risk of VTE was reportedly lower with the DARA regimen than with the non-DARA regimen [7]. However, the underlying mechanism is unclear and may be the "on target, of tumor" effect of CD38 inhibition [7]. In vitro studies have shown that CD38 deficiency can inhibit platelet activation induced by thrombin [7,104]. Animal models have shown prolonged bleeding time and unstable thrombosis in CD38-deficient mice [7,104]. Therefore, platelet dysfunction caused by CD38 deficiency may be the protective mechanism of VTE [7]. Furthermore, thrombocytopenia was a common adverse event with the DARA regimen, which may also be responsible for the low incidence of VTE [7,77–79]. At present, the mechanism of thrombocytopenia caused by dara has not been elucidated, but several hypotheses of CD20 monoclonal antibodies (rituximab) causing thrombocytopenia have been reported, which we speculate may be similar to the mechanism caused by dara: (1) rituximab triggers complement activation through C1q and leads to the destruction of platelet. (2) By harming the spleen endothelium, rituximab initiates the activation and clumping of platelet, leading to a subsequent reduction in platelet count. (3) Anti-CD20 antibodies exist in the patients [105]. However, further studies are needed.

2.4. Histone deacetylase inhibitors

Histone deacetylases (HDACs), which decrease tumor suppressor gene expression, are overexpressed in MM, resulting in increased tumor cell growth and proliferation [106]. Histone deacetylase inhibitors (HDACis) are new drugs developed in recent years, and panobinostat (LBH589) is a promising HDACi [106]. Thrombocytopenia is a common adverse event [80,81]. The underlying mechanism may be that LBH589, by inducing tubulin hyperacetylation, may cause megakaryocytes to become stiff and less dynamic and therefore unable to form the structures required for platelet formation [107]. And in megakaryocytes, Rho-GTPases proteins RhoA, Rac1 and CDC42 regulate the phosphorylation of myosin light chain (MLC) to form phospho-MLC and proplatelets [108]. In the study by Bishton et al., HDACIs treatment reduced the levels of these three proteins in mice, and reduced the ability of CDC42 and rac1 to activate P21-activated kinase1 (PAK1), which weakened the inhibitory effect of PAK1 on MLC kinase, leading to increased pMLC levels

and reduced proplatelet formation [108]. However, thrombocytopenia is reversible, and a delayed or reduced dose of panobinostat is sufficient to treat thrombocytopenia [109,110].

2.5. Immunomodulatory drugs

Immunomodulatory drugs (IMiDs) are one of the main drugs in the treatment of MM, and aromatase degradation might be the molecular process behind thrombocytopenia caused by IMIDs [11,111,82]. Aromatase, crucial for estradiol biosynthesis, emerges as a novel cereblon neosubstrate, with estradiol being crucial in the formation of proplatelets [111]. IMiDs facilitate the attraction of aromatases to the cereblon, trigger their breakdown through the ubiquitin-proteasome route, and block the formation of proplatelets in megakaryocytes that rely on autocrine estradiol signaling [11,111].

The mechanism by which IMiDs cause thromboembolism is still unclear [46]. At present, it is believed that the activation of endothelial cells and increased cytokine levels are the main causes of IMiDs promoting thromboembolism [46]. IMiDs up-regulate the levels of platelet activator cathepsin G, FVIII and VWF, inhibit the production of cyclooxygenase-2 (COX-2) and the synthesis of prostaglandin E2 (PGE2), and increase the stress and injury of endothelial cells [30]. Moreover, by enhancing the expression of phosphatidylserine (PS), TF and activating glycoprotein GPIIb/IIIa (PAC-1), and inhibiting the expression of endothelial protein C receptor (EPCR) and thrombomodulin, it leads to an imbalance between procoagulant and anticoagulant on the surface of endothelial cells [30]. Lenalidomide exhibits properties that modulate the immune system and elevate levels of inflammatory cytokines like TNFα and IL-8 [112]. The synthesis of TNFα is intimately linked to the creation of TNFα convertase (TACE, or ADMM17), culminating in an increase in soluble endothelial protein C receptor (sEPCR) levels [112]. sEPCR has the capability to rival cell surface EPCR in attaching to activated protein C (PC) and preventing PC activation, making it a potential biomarker for cancer-induced hypercoagulability in cancerous growths [112]. Nonetheless, a prior study has indicated that lenalidomide's anti-inflammatory properties could be linked to its capacity to inhibit TNFα production in peripheral blood cells [112]. Consequently, additional research is required to determine the existence of a direct link between TNFα and sEPCR [112].

2.6. Proteasome inhibitors

Bortezomib was not associated with thrombosis. It does not cause an increased risk of VTE when used alone or in combination with IMIDS, but results in a low incidence (0 %–5 %) and may actually have thromboprotective properties [30]. Several mechanisms may be responsible for the reduced risk of VTE associated with bortezomib [11,13,30]. First, bortezomib can not only block the production of platelets by inhibiting the RhoA/ROCK pathway in megakaryocytes, but also inhibit adenosine diphosphate (ADP), epinephrine and ristomycin-induced platelet aggregation, reduce the expression of P-selectin on the surface of platelets, inhibit the expression of endothelial cell adhesion molecules and transferrin induced by TNF-α, thus having a certain degree of antithrombotic effect [11,13,113]. Additionally, bortezomib enhances the expression of endothelial thrombomodulin by activating Kruppel-like transcription factor, thereby boosting endothelial cells' ability to generate APC, and it can also inhibit the reduction of thrombomodulin due to inflammatory cytokines [30].

TMA is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and end-organ damage [114]. It can also be caused by proteasome inhibitors (PIs) [46,83]. A complex process contributing to the development of TMA caused by carfilzomib has been reported [115]. Diagnosing multiple myeloma stands as the initial risk element [115]. Mutations in the alternate complement pathway constitute the second risk element [115]. Studies have shown that mutations in genes of the alternative complement pathway could contribute to TMA caused by carfilzomib [115]. The last influencing element is the diminution of vascular endothelial growth factor (VEGF) [115]. PIs focus on the ubiquitin-proteasome pathway, thereby safeguarding pro-apoptotic elements against breakdown [115]. Additionally, they fortify the nuclear factor kappa B (NFκB) complex, obstructing its movement to the nucleus, reducing subsequent signaling, and hindering VEGF transcription [115]. Therefore, local VEGF production by renal epithelial cells is reduced [115]. Consequently, there's a decrease in local complement regulatory proteins, rendering endothelial cells susceptible to complement activation. A mix of the aforementioned risk elements would essentially foster an environment favorable to TMA [114,115].

2.7. Bcl-2 inhibitor

In MM, research indicates that the bone marrow microenvironment triggers an increase in antiapoptotic BCL-2 family proteins, enhancing the survival of MM cells [116]. And inhibition of BCL-2 can lead to apoptosis in MM cells. Venetoclax (Ven) is a highly selective and potent oral BCL-2 inhibitor that triggers MM cells death [116]. Notably, t (11; 14) translocation MM cells, which are rely heavily on BCL-2 protein for survival, exhibit particular sensitivity to VEN-induced apoptosis [116,84]. In studies of venetoclax monotherapy in patients with RRMM, common adverse events were gastrointestinal toxicity and grade 3/4 hematologic toxicity, with thrombocytopenia occurring in 26 % of patients [85]. However, these toxicities were manageable and didn't lead to discontinuation of treatment [85]. At present, there are no related studies on the mechanism of ven causing thrombocytopenia and thrombotic events reported, and further studies are needed.

2.8. Therapeutic strategies for MM with bleeding or thrombosis complications

Therapies for symptomatic control of bleeding complications encompass mass red blood cell and platelet transfusions, coagulation factor replacement, antifibrinolytic drugs, protamine sulfate, arginine, vasopressin, vitamin K, folic acid therapy, and platelet factor 4

[5]. In patients with dysfibrinogenemia, high-dose chemotherapy or therapeutic plasmapheresis can be selected to relieve symptoms or potential coagulopathy [117]. In refractory cases, replacement of chemotherapy regimen, plasmapheresis and splenectomy can be considered [117,118]. However, symptomatic treatment can only temporarily stabilize the patient's condition. To effectively mitigate bleeding, treatment strategies must fundamentally address the etiology of the main disease [5].

For VTE in MM, patients should be stratified according to VTE risk before choosing drugs to prevent thrombosis [119]. Recently, several risk assessment models have been developed and verified, such as IMPEDE VTE, SAVED and PRISM score [120]. However, the IMPEDE VTE and PRISM scores can be used for patients who receive any targeted therapy induction of myeloma, and the SAVED score is only used for patients treated with IMiDs (Table 3) [120]. The thromboprophylaxis options include aspirin, low-molecular-weight heparin (LMWH), warfarin, vitamin K antagonists, or direct oral anticoagulants (DOACs) [67,119]. The National Comprehensive Cancer Network Multiple Myeloma Treatment Guidelines recommend the use of the IMPEDE VTE and SAVED scores to assess VTE risk in newly diagnosed patients starting chemotherapy [120]. And aspirin thrombosis prevention is recommended for those with low-risk scorers, while antithrombotic thrombosis prevention (such as low-dose DOACs and LMWH) is recommended for those with middle-risk or high-risk scorers [120]. For thrombotic treatment, DOACs and LMWH are equally effective [6], but appear to be more effective than aspirin [121]. And there were no differences in efficacy or safety among different DOACs agents [6,122]. Therefore, the choice of treatment is based on the characteristics of the patients, especially in the case of renal insufficiency, and apixaban is preferred [6].

Drug prevention of arterial thrombosis is uncertain, and anticoagulants seem to be more effective than aspirin [6]. But in the concern of bleeding complications risk, aspirin may be a safer choice [67]. Dietary prevention is also important. This is because obesity is a risk factor for increased mortality in MM [123,124] and is the only known modifiable risk factor [53]. Therefore, a low-fat diet and regular monitoring of lipid levels are particularly crucial for MM patients [53].

3. Conclusion

MM is a disease predisposed to coagulation and bleeding. The risk and pathogenesis of bleeding and thrombosis in MM are multifaceted. Many drugs, including new drugs, increase the risk of hemorrhage and blood coagulation. Using risk assessment tools to stratify patients and selecting drugs such as aspirin or low molecular weight heparin according to international guidelines is an important step to prevent and treat bleeding and thrombotic complications. DOACs are becoming more and more favoured in clinical practice because of their good clinical performance and convenience without the need for routine monitoring. As a result, DOACs are expected to become the primary thromboprophylaxis.

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Data availability statement

No data were used for the research described in this article.

Table 3
Risk assessment models.

IMPEDE VTE Score	SAVED score	PRISM score
Immunomodulatory drug: +4		
Body mass index ≥25 kg/m2: +1		
Pathologic fracture pelvis/femur: +4	Surgery within last 90 days: +2	
Erythropoiesis-stimulating agent: +1	Asian race: -3	Prior history of venous thromboembolism: +8
Dexamethasone (High-dose, ≥1600 mg/cycle): +4	VTE history: +3	Race (Black race): +1
Dexamethasone Low-Dose (<160 mg/cycle): +2	Eighty (age ≥80 years): +1	Immunomodulatory use in induction therapy: +2
Doxorubicin: +3	Dexamethasone (high dose): +2	Surgery within 90 days: +5
Ethnicity/race: Asian race: -3	Dexamethasone (low dose): +1	Abnormal Metaphase Cytogenetics: +2
VTE history: +5		
Tunnelled line/CVC: +2		
Existing therapeutic warfarin or LMWH use: -5		
Existing prophylactic aspirin or LMWH use: -3		
Stratified risk groups		
Low risk: score ≤3	Low risk: score ≤1	Low risk: score 0
Intermediate risk: score 4-7	High risk: score ≥2	Intermediate risk: score 1-6
High risk: score ≥8		High risk: score ≥7

CVC, central venous catheter; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

CRediT authorship contribution statement

Yudie Huang: Writing – original draft, Conceptualization. **Chongyu Wang:** Writing – original draft. **Hua Wang:** Writing – original draft. **Hong Liu:** Writing – review & editing, Validation, Supervision. **Lu Zhou:** Writing – review & editing, Validation, Supervision, Conceptualization.

Declaration of competing interest

The authors declare no conflicts of interest.

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