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Review

Venous thromboembolism in multiple myeloma: Current perspectives in pathogenesis

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ABSTRACT

Patients with multiple myeloma are at increased risk of venous thromboembolism (VTE) compared to the general population. The introduction of immunomodulatory agents, such as thalidomide and lenalidomide, substantially increases the incidence of VTE in multiple myeloma patients, especially when used in combination with high-dose dexamethasone and/or anthracycline-based chemotherapy. Thromboprophylaxis is recommended for reducing VTE in patients receiving immunomodulatory agent-based regimens. On the other hand, bortezomib, a proteasome inhibitor, is not associated with an increased risk of VTE, as observed by a very low incidence of thrombotic complications in the absence of thromboprophylaxis. Currently, the mechanisms underlying the impact of these agents on VTE are not well-understood. Further studies to investigate the pathogenesis of VTE in multiple myeloma are warranted. These studies may not only yield greater insight into the pathogenesis of disease but may also define novel targets for the prevention and treatment of thromboembolic events in patients with multiple myeloma.

1. Introduction

Multiple myeloma is a clonal plasma cell neoplasm accounting for 15% of haematologic malignancies and 1% of all cancers. There are approximately 20,000 new cases and 10,000 estimated deaths per year in the United States.[1,2] Multiple myeloma remains an incurable disease, but the advent of novel agents, such as immunomodulatory drugs (IMiDs) and proteasome inhibitors, has significantly improved clinical outcomes including survival.[3] However, IMiD administration has been associated with a remarkable rise in the incidence of thromboembolic events.[4,5] Although a recent retrospective study demonstrated that venous thromboembolism (VTE) development in patients with multiple myeloma who received lenalidomide and high-dose dexamethasone did not affect overall survival and time to progression, this may be explained by the favourable impact of lenalidomide on survival.[6] Furthermore, despite the absence of data that VTE impacts survival in multiple myeloma, it could certainly have an impact on the quality of life and the cost of treatment.

Previously, thromboembolic events were less emphasised than bleeding complications in patients with haematologic malignancy. However, a recent large population-based study demonstrated that patients with haematologic malignancy, especially multiple myeloma, carry the highest risk of VTE – up to 28-fold compared to persons without malignancy

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– followed by lung cancer and gastrointestinal cancer.[7] Furthermore, a large hospital-based study of deep vein thrombosis (DVT) risk during the pre-era of novel therapies for multiple myeloma that included more than 4 million hospitalised veterans demonstrated that plasma cell disorders were associated with an increased risk of DVT.[8] The crude DVT rate after diagnosis of monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma was 3.1 per 1000 person-years (relative risk [RR] = 3.3, 95% confidence interval [CI], 2.3–4.7), and 8.7 per 1000 person-years (RR = 9.2, 95% CI, 7.9–10.8), respectively, compared to 0.9 per 1000 person-years of the general population of hospitalised veterans.

MGUS is a benign clonal plasma cell disorder that can progress to multiple myeloma. However, a prospective study demonstrated that patients with MGUS were at increased risk for VTE. The incidence of VTE in this cohort was 6.1% after a median follow-up of 44 months.[9] Collectively, these findings indicate the presence of a 'hypercoagulable state' in patients with clonal plasma cell disorders.[8,10]

2. Epidemiology of thrombotic complications of therapeutic agents in multiple myeloma

Prior to the era of novel therapies, melphalan, corticosteroids and anthracyclines were commonly employed drugs used in the treatment of multiple myeloma. Although these drugs ameliorate clinical symptoms, they do not significantly improve survival. Thromboembolism was not recognised as a major complication of multiple myeloma until the advent of IMiDs. As a basis for comparison, the incidence of VTE in multiple myeloma patients in both newly diagnosed and relapsed/refractory cases receiving common conventional therapies, such as melphalan–prednisone, dexamethasone and vincristine–doxorubicine–dexamethasone, was 27% in the absence of thromboprophylaxis.[13,14,16–25] Thalidomide, the first IMiD available for the treatment of multiple myeloma, was introduced in 1999, followed by lenalidomide in 2002.[11] The advent of these novel agents has significantly improved survival in multiple myeloma both in the recent diagnosis and in the relapsed/refractory setting.[3] However, early phase clinical trials evaluating the efficacy and safety of IMiDs demonstrated a very high incidence of VTE. Subsequently, various thromboprophylactic agents have been incorporated into IMiD-based treatment protocols.[12–15] By contrast, bortezomib, a proteasome inhibitor, was found to improve patient outcomes without an increased incidence of VTE.

2.1. *Thalidomide*

Thalidomide itself increases the risk of VTE only modestly. The incidence of VTE in multiple myeloma patients receiving thalidomide alone was 5% or less in patients with both newly diagnosed and relapsed/refractory diseases.[26–30] A recent meta-analysis demonstrated that thalidomide, dexamethasone and their combination increased the risk of VTE among multiple myeloma patients by 2.6-, 2.8- and 8-fold, respectively.[4] In other studies, the combination of thalidomide and dexamethasone in the absence of thromboprophylaxis increased the incidence of VTE to 11.5–26% in newly diagnosed multiple myeloma patients,[13,20–22,31] and to 2–8% in relapsed/refractory cases.[32,33] The combination of anthracycline and thalidomide was associated with the higher VTE rates, varying from 1058% in the absence of thromboprophylaxis.[12,34–37]

2.2. *Lenalidomide*

Lenalidomide, a member of the second generation of IMiDs, showed significant activity in multiple myeloma with encouraging results in phase I and phase II clinical trials. The incidence of VTE in relapsed/refractory multiple myeloma patients receiving lenalidomide alone was 3–5%.[38,39] However, the combination of lenalidomide and high-dose dexamethasone in the absence of thromboprophylaxis elevated the VTE rate to 26–75% in newly diagnosed multiple myeloma patients[15,40] and to 11–15% in relapsed/refractory patients.[24,25] Data presented from a phase III study of lenalidomide in combination with high-dose versus low-dose dexamethasone in newly diagnosed multiple myeloma patients demonstrated that the dose of dexamethasone was significantly associated with the risk of thrombosis. In this study, the incidence of VTE in patients receiving lenalidomide plus low-dose dexamethasone was 12%, whereas the incidence was increased to 26% in patients receiving the combination of lenalidomide and high-dose dexamethasone.[40]

2.3. *Bortezomib*

Bortezomib is the first proteasome inhibitor approved for the treatment of multiple myeloma. A clinical trial demonstrated very promising outcomes in relapsed/refractory multiple myeloma patients, leading to its rapid approval by the US FDA.[41] Subsequent studies demonstrated an improvement in patient outcomes in both newly diagnosed and relapsed/refractory settings. Notably, the incidence of VTE in patients receiving bortezomib with other therapeutic agents in the absence of thromboprophylaxis was less than 4%.[18,23,42–50] These findings suggest that IMiDs promote the development of thrombosis, whereas bortezomib may paradoxically provide a protective advantage against the thrombogenic potential of other drugs and underlying disease state (Fig. 1).

2.4. *Erythropoietic stimulating agents*

Erythropoietic stimulating agents (ESAs) are commonly used for ameliorating anaemia in patients with cancer, including multiple myeloma. However, several large clinical trials and meta-analyses have demonstrated that ESA administration is associated with an increased incidence of VTE as well as mortality in cancer patients.[51,52] A retrospective analysis from a phase III clinical trial demonstrated that concomitant ESA therapy was an independent risk factor for VTE in patients with multiple myeloma. Concomitant ESA therapy increased the incidence of VTE from 5% to 23% in multiple myeloma patients receiving lenalidomide plus high-dose dexamethasone and from 1% to 7% in patients receiving high-dose dexamethasone alone.[53] Furthermore, ESA administration was significantly associated with poorer clinical outcomes including overall survival and progression-free survival in multiple myeloma.[54] Although other studies did not support the detrimental impact of ESAs on clinical outcomes, ESAs should be

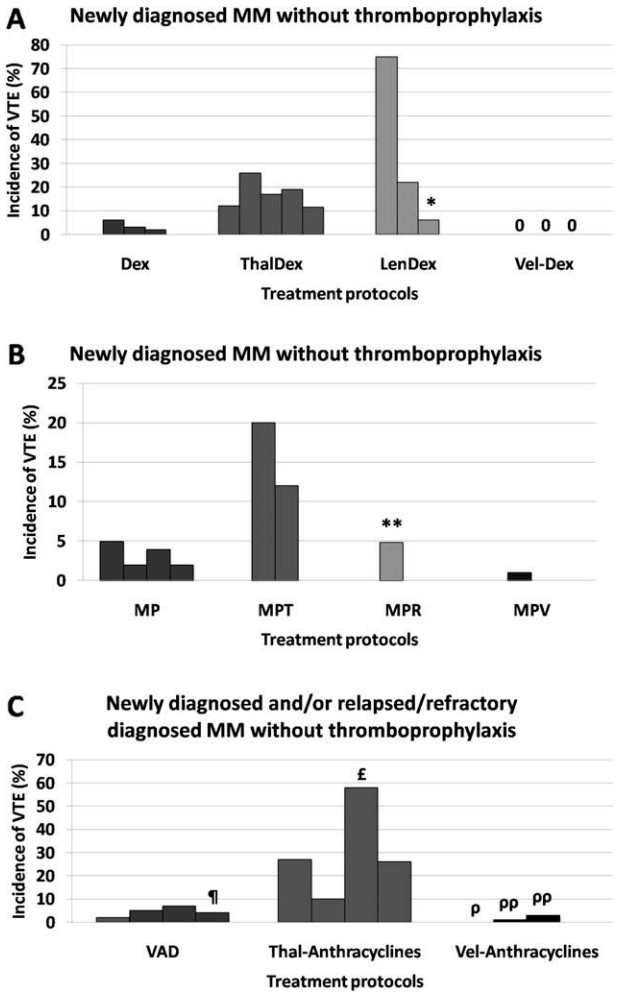

Fig. 1 – The incidence of VTE in newly diagnosed multiple myeloma patients receiving treatment without thromboprophylaxis. (A) High-dose dexamethasone-containing regimens.[13,15,16,20–22,31,40,42,44,46] (B) Melphalan-prednisone-containing regimens.[14,16–18,109] (C) Anthracycline-containing regimens.[12,13,19,20,34–36,44,45,50] Dex: dexamethasone, Thal and T: thalidomide, Len and R: lenalidomide (revlimid™), Vel and V: bortezomib (Velcade™), M: melphalan, P: prednisone, VAD: vincristine, doxorubicin, dexamethasone, *low-dose dexamethasone, **aspirin 100 mg/day as a thromboprophylaxis, ¶dexamethasone, vincristine and pegylated liposomal doxorubicin, £newly and relapsed/refractory patients, ρnewly diagnosed patients, ρρrelapsed/refractory patients.

prescribed with high caution in patients with multiple myeloma.[55,56] Recently, the American Society of Hematology/the American Society of Clinical Oncology published updated clinical practice guidelines of ESA therapy in patients with cancer.[57]

3. Mechanisms of venous thromboembolism in multiple myeloma

The mechanisms of VTE in multiple myeloma have not been well established either *in vitro* or *in vivo*. Several studies demonstrate that surgery, hospitalisation, central venous catheters, prior history of VTE and medical co-morbidities are risk factors for VTE in cancer patients.[58] However, there is a limited evidence supporting the impact of these factors on VTE risk in multiple myeloma patients. One large retrospective study demonstrated that a previous history of VTE, family history of VTE and a known hypercoagulable state were correlated with VTE development in patients with multiple myeloma, while by univariate analysis history of VTE, family history of VTE and immobilisation were risk factors in patients with MGUS.[9] Another retrospective study demonstrating factors independently associated with an increased risk of VTE were light chain disease, a recent diagnosis of multiple myeloma, therapy with thalidomide, high CRP levels and acquired activated protein C resistance.[59] Hypothesised mechanisms include underlying genetic thrombophilia, the prothrombotic state associated with multiple myeloma itself, impairment of endogenous anticoagulation and fibrinolytic pathways and thrombogenic potential of treatment (Fig. 2). The evidence for each of these possible mechanisms will be reviewed in brief.

3.1. *Genetic risk factors for VTE*

Cancer patients who carry the factor V Leiden mutation have a 12-fold increased risk of VTE compared with individuals absent for both conditions.[7] However, there have not been large studies evaluating a connection between inherited risk factors and the development of VTE in multiple myeloma.

A recent study analysing 3400 single nucleotide polymorphisms (SNPs) in multiple myeloma patients after thalidomide exposure identified several SNPs associated with an increased risk of thalidomide-associated VTE, including SNPs associated with genes involved in the pathways of drug transport/metabolism, DNA repair and cytokine balance such as *CHEK1*, *XRRC5*, *LIG1*, *ERCC6*, *NFKB1*, *TNFRSF17* and *CASP3*.[60] These findings encourage further studies to investigate genetic risk factors contributing to the pathogenesis of multiple myeloma and VTE in patients receiving thalidomide, in an effort to uncover novel genetic risk factors, and identify those patients at high risk of VTE who require more aggressive prophylaxis.

3.2. *Prothrombotic state associated with multiple myeloma*

Patients with multiple myeloma have higher levels of endogenous thrombin potential (ETP) in a global assay of thrombin generation, irrespective of thalidomide treatment.[61] Several studies in the general population have demonstrated that patients with increased ETP were associated with an increased risk of a first VTE as well as recurrence.[61–64] However, no study has reported a correlation between increased ETP and the development of VTE in multiple myeloma.

Patients with multiple myeloma have increased von Willebrand factor (vWF) antigen, factor VIII coagulant activity and fibrinogen levels compared to normal controls.[65–67] These elevated coagulation factor levels were associated with more advanced stages of disease. The relationship between increased levels of these procoagulant factors and thrombosis remains unclear because of the small number of patients that were analysed. Larger prospective studies are required to establish

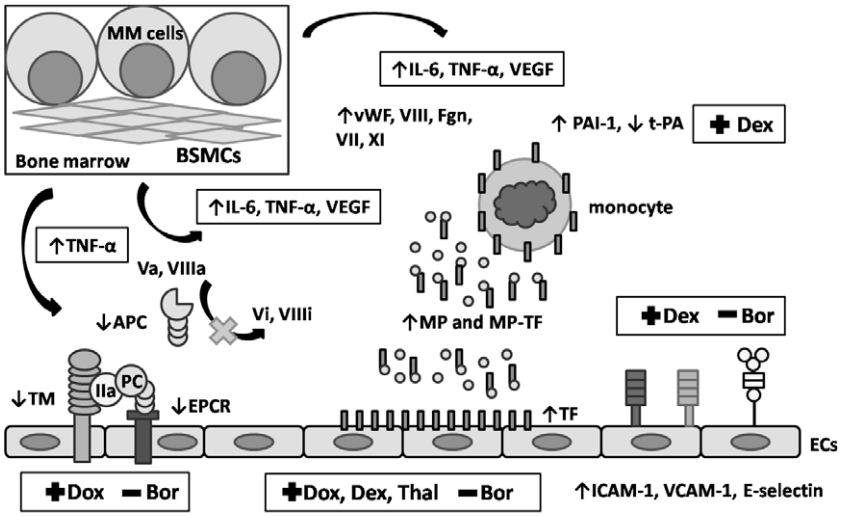

Fig. 2 – Possible mechanisms of the hypercoagulable state in multiple myeloma and thrombogenic effects of anti-multiple myeloma therapy. Several cytokines and signalling molecules in multiple myeloma are able to up-regulate procoagulant factors, such as vWF, VIII, fibrinogen, TF and MP-TF and PAI-I, while down-regulating thrombomodulin, EPCR, APC and t-PA, resulting in an increased activation of coagulation, dysregulation of endogenous anticoagulation and impairment of fibrinolysis. Common therapeutic drugs used in the treatment of multiple myeloma, such as thalidomide, dexamethasone and doxorubicin, not only further impair the function of endogenous anticoagulation and fibrinolytic pathways but also enhance the expression of several cellular adhesion molecules. By contrast, bortezomib enhances endothelial thrombomodulin expression, while down-regulating the expression of TF and cellular adhesion molecules on endothelial cells that may be potentially protective for VTE in multiple myeloma. MM cells: multiple myeloma cells, BMSCs: bone marrow stromal cells, IL-6: interleukin-6, TNF-α: tumour necrosis factor-α, VEGF: vascular endothelial growth factor, vWF: von Willebrand factor, VIII: factor VIII, VII: factor VII, XI: factor XI, Va: activated factor V, Vi: inactivated factor V, VIIIa: activated factor VIII, VIIIi: inactived factor VIII, fgn: fibrinogen, t-PA: tissue-plasminogen activator, IIa: thrombin, PC: protein C, APC: activated protein C, TM: thrombomodulin, EPCR: endothelial protein C receptor, ICAM-1: intercellular adhesion molecule-1, VCAM-1: vascular adhesion molecule-1, TF: tissue factor, MP: microparticle, MP-TF: microparticle-associated tissue factor, Dox: doxorubicin, Dex: dexamethasone, Thal: thalidomide, Bor: bortezomib, ✚ thrombogenic potential, ▬ thromboprotective potential.

whether the increases in these coagulation factors are associated with an increased risk of VTE in patients with multiple myeloma.

The tissue factor (TF)-factor VIIa complex is the primary initiator of coagulation *in vivo*. TF appears to play several important roles in cancer including promotion of thrombosis, metastasis, angiogenesis and tumour progression. Its expression increases in several types of non-haematologic malignancies, including glioma, pancreatic cancer, non-small cell lung cancer, colorectal cancer, renal cell carcinoma, ovarian cancer, prostatic cancer and breast cancer.[68] However, the role of TF in multiple myeloma has not been studied in detail. An early study showed an increased expression of TF in haematologic malignancies, especially leukaemic blasts in acute myeloid leukaemia and platelet-associated TF microparticle in polycythemia vera and essential thrombocythemia.[69] By contrast, a recent study demonstrated that the hypercoagulable state in haematologic malignancies was not associated with increased levels of circulating TF antigen or TF mRNA. However, this study population was heterogeneous comprising 93 patients with non-Hodgkin lymphoma (52%), acute myeloid leukaemia (22%), chronic lymphocytic leukaemia (15%) and multiple myeloma (12%).[70] Moreover, this study measured TF antigen only, which may not correlate with TF activity.[71] A recent study evaluating microparticle-associated tissue factor (MP-TF) activity in 123 untreated multiple myeloma patients demonstrated significantly increased MP-TF activity levels compared to normal volunteers. Although MP-TF activity levels decreased significantly after initiation of chemotherapy on average, they remained persistently elevated in patients who developed VTE during induction chemotherapy.[72] Notably, the source of increased circulating TF activity in multiple myeloma has not been determined. Several important cytokines and transcription factors that are elevated in patients with multiple myeloma, such as IL-6, TNF-α, VEGF and NF-κB, are able to increase TF expression on both monocytes and endothelial cells.[73–77] In addition, the regulation of TF by NF-κB p50 is probably important in the pathogenesis of DVT, as inhibition of NF-κB can reduce TF expression and DVT in a mouse model.[77] Further studies are required to investigate the role of TF in the pathogenesis of VTE in multiple myeloma.

3.3. *Dysregulation of anticoagulation and impairment of fibrinolysis*

Several studies have reported the presence of abnormalities in the endogenous anticoagulation pathways in multiple

myeloma. Acquired activated protein C resistance in the absence of the factor V Leiden mutation is a common finding in patients with multiple myeloma, and it is associated with an increased risk of VTE.[59,78–80] Alterations of antithrombin, protein C and protein S levels in multiple myeloma were observed in various studies. Patients with multiple myeloma had decreased protein S and protein C levels, whereas no reduction of antithrombin levels was found.[59,65,81,82] The role of thrombomodulin in the pathogenesis of VTE in multiple myeloma remains unclear. While an early study demonstrated significantly reduced plasma-soluble thombomodulin levels in the first month of thalidomide–dexamethasone therapy,[82] a subsequent report from the same investigators observed that soluble thrombomodulin levels were lower in patients with multiple myeloma than those in normal controls, and were not modified by thalidomide therapy.[83] A reduced expression of thrombomodulin and also endothelial protein C receptor (EPCR) on endothelial cells may be induced by TNF-α.[84] By contrast, a recent study showed increased soluble thrombomodulin levels in multiple myeloma patients unrelated to thalidomide.[61] Further studies are required to clarify the role of thrombomodulin in the pathogenesis of multiple myeloma-related and thalidomide-related thrombosis.

Patients with multiple myeloma demonstrate impaired fibrinolytic activity. The M-protein may interfere with fibrin clot formation, resulting in abnormally thin fibrin fibres, and delayed fibrinolysis.[85,86] The fibrinolytic rate of a thrombus appears to be faster for clots composed of thicker fibres compared to clots composed of thinner fibres.[87] Furthermore, patients with multiple myeloma have significantly increased IL-6, CRP and plasminogen activator inhibitor-1 (PAI-1) levels compared to normal subjects.[88] In addition, a recent phase III study demonstrated that both thalidomide- and non-thalidomide-containing regimens used for induction therapy induced hypofibrinolysis that may potentiate the prothrombotic state.[89] The impaired fibrinolytic activity during the induction therapy may be explained by the effect of these agents on up-regulation of PAI-1.

3.4. *Thrombogenic potential of anti-multiple myeloma therapy*

3.4.1. *Dexamethasone*

Dexamethasone has been the backbone of treatment in multiple myeloma patients eligible for transplantation for several decades. It induces apoptosis in multiple myeloma cells through glucocorticoid response element transactivation.[90] Pleiotropic effects of dexamethasone on the haemostatic system have been addressed in several studies. Early studies showed that dexamethasone increased lipopolysaccharide-induced TF expression on monocytes by stabilising TF mRNA.[91,92] A recent study demonstrated that high-dose dexamethasone also enhanced the expression of TF, as well as cellular adhesion molecules (ICAM-1, VCAM-1, and E-selectin) and vWF, while down-regulating thrombomodulin and urokinase on endothelial cells.[93] Furthermore, dexamethasone was able to up-regulate PAI-1, while down-regulating t-PA, resulting in a decrease of fibrinolytic activity.[94,95]

3.4.2. *Anthracyclines*

Doxorubicin is the most commonly used anthracycline in the treatment of several cancers, including multiple myeloma. It causes DNA damage, and induces apoptosis by various mechanisms.[96] Other anthracyclines used in the treatment of multiple myeloma include pegylated liposomal doxorubicin and epirubicin. An *in vitro* study demonstrated that endothelial cells and monocytes treated with doxorubicin and epirubicin promoted increased thrombin generation. Specifically, doxorubicin and epirubicin elevated TF activity by increasing cell-surface exposure of phosphatidylserine.[97] Furthermore, doxorubicin-free radical metabolites interfered with the protein C anticoagulant pathway by reducing cell-surface EPCR levels via down-regulation of EPCR mRNA levels. The net effect was a decreased capacity of endothelial cells to activate protein C.[98]

3.4.3. *Thalidomide*

Thalidomide is the prototype of the IMiDs, showing significant activity against multiple myeloma. Thalidomide and its analogues directly induce apoptosis or growth arrest of multiple myeloma cells, alter the interaction of tumour cells and bone marrow stromal cells, inhibit the production of various cytokines, such as IL-6 and VEGF in the bone marrow microenvironment and stimulate anti-multiple myeloma immunity mediated by natural killer cells.[99] There is a little evidence to explain the thrombogenic potential of IMiDs. In the cell culture model, thalidomide alone modestly stimulated TF activity in monocytes. However, after priming cells with TNF-α, thalidomide markedly induced TF activity greater than 10-fold compared to unstimulated cells.[100] Taken together, these effects may explain the thrombogenic effects of thalidomide when combined with dexamethasone and/or anthracyclines in the pathogenesis of VTE in multiple myeloma (Fig. 2).

3.4.4. *Bortezomib*

Bortezomib is the first proteasome inhibitor approved for treatment in both newly diagnosed and relapsed/refractory multiple myelomas. The mechanisms of actions of bortezomib are complex and not well-understood. Preclinical studies demonstrated that this agent directly inhibits proliferation of multiple myeloma cells, induces apoptosis, alters myeloma-stromal cell interaction and abrogates several paracrine effects in the bone marrow microenvironment.[101] Interestingly, the incidence of VTE in bortezomib-containing regimens is very low regardless of the patient status or the drug regimen to which it is added. The exact mechanism behind the apparent anti-thrombogenic properties of bortezomib has not been clearly defined.

One *in vitro* study demonstrated an inhibitory effect of bortezomib on platelet aggregation induced by ADP, and ATP-release reaction,[102] while an *in vivo* study also demonstrated that bortezomib inhibited platelet aggregation stimulated by ADP, ristocetin and epinephrine.[103] A recent *in vitro* study evaluated the effects of bortezomib on endothelial cells. Bortezomib significantly up-regulated endothelial thrombomodulin expression and enhanced the capacity of endothelial cells to activate protein C via the induction of Krüppel like

factor (KLF) 2 and KLF4. In addition, bortezomib significantly suppressed TNF-α mediated the induction of E-selectin, VCAM-1, ICAM-1 and TF on endothelial cells.[104] The KLFs are members of a zinc finger family of transcription factors that function as important regulators of endothelial gene expression and cellular function.[105] Overexpression of both KLF2 and KLF4 is able to enhance endothelial thrombomodulin expression, while suppressing cytokine-mediated induction of TF.[106,107] Furthermore, a previous study demonstrated that degradation of KLF4 in a human colon cancer cell line was mediated via the proteasome pathway, and could be reversed by proteasome inhibitors.[108] This is the first study to demonstrate a putative anti-thrombotic mechanism of action of bortezomib. However, another recent study demonstrated that bortezomib significantly induced activation of canonical NF-κB, p50 and p65, in both multiple myeloma cells and peripheral blood mononuclear cells.[109] This finding is antithetical to the previous hypothesis that bortezomib is a potent NF-κB inhibitor as evidenced by down-regulation of tumour expression of NF-κB transcriptional targets such as IL-6.[110,111] Whether bortezomib inhibits endothelial TF expression remains to be determined. Moreover, there have not been any studies directly investigating the modulatory effects of bortezomib on the haemostatic system when combined with other anti-multiple myeloma agents either *in vitro* or *in vivo*. Therefore, whether these observations explain how bortezomib overcomes the thrombogenic effects of both the underlying disease and that induced by other therapeutic agents requires further study.

4. Prophylaxis of venous thromboembolism in multiple myeloma

Both thalidomide and lenalidomide markedly increase the risk of VTE when combined with other chemotherapeutic agents. Therefore, an effective thromboprophylaxis strategy is recommended for reducing the risk of VTE in patients receiving IMiDs. Low molecular weight heparin (LMWH), aspirin and warfarin have been investigated in several clinical trials. However, there have not been any randomised controlled trials directly comparing the efficacy of these agents. Most current recommendations and reviews related to prevention of thrombosis in multiple myeloma are based on limited evidence.

LMWH has demonstrated efficacy in the prevention of VTE in several clinical trials. Prior to mandatory prophylaxis, 13 VTE events were observed in 65 patients (20%) with multiple myeloma receiving melphalan–prednisone–thalidomide. With institution of LMWH, only 2 VTE events were observed in 64 (3%) subsequent patients.[14] Similarly, other studies have shown that LMWH reduced the VTE rate in patients receiving thalidomide-containing protocols, while fixed-low-dose warfarin failed to decrease this complication.[112,113] By contrast, one clinical trial demonstrated that fixed-low-dose warfarin effectively decreased the incidence of VTE in patients receiving thalidomide–dexamethasone from 26% to 12%.[13] Two recent clinical trials also demonstrated the efficacy of LMWH in the prevention of VTE in patients treated with lenalidomide-based regimens compared to historical controls.[114,115]

Generally, aspirin is considered to be less effective than anticoagulants in the prevention of VTE, and an expert consensus recommends against the use of aspirin alone as thromboprophylaxis for any patient group.[116] However, several clinical trials have shown promising results of aspirin in VTE prophylaxis in multiple myeloma patients receiving thalidomide as well as lenalidomide.[15,35,115,117,118] One phase 2 study demonstrated that daily low-dose aspirin use as thromboprophylaxis in patients with multiple myeloma receiving pegylated doxorubicin, vincristine, dexamethasone and thalidomide was associated with a lower risk of VTE (hazard ratio = 0.22, 95% CI, 0.10–0.47, $p < 0.001$) compared to patients who did not receive thromboprophylaxis.[35] These findings may indicate a role of platelets in the pathogenesis of VTE associated with IMiD therapy in multiple myeloma.

Limited data are available for evaluating the efficacy of warfarin for the prevention of VTE in multiple myeloma patients receiving IMiDs. Only one small clinical trial with 26 patients showed that both full-dose warfarin and LMWH were equally effective in the prevention of VTE in patients receiving thalidomide–dexamethasone.[119] Large randomised controlled trials to directly compare the efficacy of thromboprophylactic regimens are critical to determine the appropriate strategy for the prevention of VTE in patients receiving IMiDs. Until then, the recommendations for prophylaxis of VTE in multiple myeloma have been published based on expert opinion according to current available data.[120–122]

5. Conclusion

Patients with multiple myeloma are at high risk for developing VTE, especially those receiving IMiDs. Even though the emergence of these novel agents significantly improves survival, it is accompanied by a substantial increase of the incidence of VTE as a major complication of treatment. The mechanisms involved in the development of thrombosis in multiple myeloma are complex, and remain poorly understood. Further studies, especially those focusing on the pathophysiology and management of this complication, are warranted.

Conflict of interest statement

None declared.

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