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Thrombosis in multiple myeloma (MM)

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Abstract

Thrombosis is a frequent feature in individuals with myeloma, particularly those treated with oral immunomodulatory drugs (IMiD) such as thalidomide or lenalidomide concomitantly with anthracyclines or dexamethasone. Up to a third of these individuals may develop venous thrombosis if not given the benefit of prophylaxis. Interestingly, in contrast to individuals with solid tumors in whom thrombosis is a marker of poor prognosis, thrombosis does not impact overall survival in patients with myeloma. This finding suggests that the mechanisms of thrombosis in hematological neoplasms may differ from solid epithelial tumors and that thrombosis in the former may be driven by therapy and not by a procoagulant phenotype of the neoplastic plasma cells. This may also explain why thrombosis in the context of IMiD-based therapy may be prevented by the use of prophylactic aspirin. In this text, we review the pathogenesis of thrombosis in myeloma, its relation to different chemotherapeutic regimens and the use of thrombo-prophylaxis.

Keywords

Thrombosis; Multiple myeloma

Introduction

Individuals with multiple myeloma (MM) are at an elevated risk of venous as well as arterial thrombosis.^{1,2} The cause of thrombosis in these individuals is a result of interaction between patient comorbidities, chemotherapy, and tumor-related factors. Interestingly, clinical evidence suggests that tumor-related pro-coagulant factors differ from those seen in patients with solid tumors.^{3–5} It is clear that thrombo-prophylaxis is warranted in some MM, particularly in patients receiving immunomodulatory drugs (IMiDs) in combination with dexamethasone. There is an emerging consensus on the efficacy of both aspirin and traditional anticoagulants in either prophylactic or therapeutic doses. The choice between aspirin, vitamin K inhibitors, and heparins must take into account the risk of thrombosis for a given patient at a given time, the potential for thrombotic risk-reduction, the risk of bleeding, and costs.

Pathogenesis of Thrombosis in MM

Besides known hereditary and acquired risk factors for thrombosis such as surgery, immobility, previous thrombosis, or advanced age, cancer in general and its treatment predisposes individuals to thrombosis. However, there are significant clinical differences between venous thromboembolic events (VTEs) associated with solid tumors and those

which occurs in patients with MM. While thrombosis is a marker of underlying aggressive tumor behavior and poor prognosis in individuals with solid tumors, this does not seem to be the case for MM. In solid tumors, Levitan *et al.* demonstrated that hospitalized patients with concurrent VTE or pulmonary embolism and malignancy have more than threefold higher risk of death than patients with VTE who do not have cancer.³ By contrast, thrombosis is not an indicator of poor prognosis in newly diagnosed or in relapsed patients with MM.^{4,5} This suggests that molecular mechanisms that are thought to be responsible for linking thrombosis and aggressive tumor behavior in solid tumors, such as expression of tissue factor, up-regulation of cyclo-oxygenase-2, and plasminogen activator inhibitor 1 by tumor cells, may not turn out to be relevant in MM-associated thrombosis.⁶

While thrombosis can be observed in all stages of the disease, its risk is particularly high in patients taking immunomodulatory drugs (the so-called IMiDs) in combination with dexamethasone. For these patients, aspirin, as shown by several groups and recently corroborated in a prospective phase III clinical trial, is effective for venous thromboprophylaxis in low thrombotic risk MM.^{7–11} Furthermore, aspirin is as effective as fixed low dose warfarin (1.25 mg/day) or prophylactic dose low-molecular-weight heparin.¹¹ In contrast, aspirin has not been shown to reduce the risk of thrombosis in individuals with solid tumors. The reason for efficacy of aspirin in MM may be partly due to platelet and endothelial cell activation, but the precise explanation is still not clear.⁷ One recent study showed high levels of promyelocyte-derived cathepsin G upon exposure to IMiDs and dexamethasone, with consequent platelet activation.¹²

Interestingly, the monoclonal gammopathy of unknown significance (MGUS) which always precedes MM, is also associated with a higher risk of VTE when the monoclonal spike is IgG or IgA, but not IgM.¹³ Since there is no clear medical indication for a serum protein electrophoresis, it is likely that a certain bias is introduced in that patients with MGUS are more likely to have other comorbid conditions that lead to the testing of the serum in search for monoclonal proteins.¹⁴ Other pro-thrombotic abnormalities that predispose individuals with MM to venous thromboembolism have also been identified, including high factor VIII levels, acquired activated protein C resistance, and hypofibrinolysis.^{15–17}

Taken together, these clinical data suggest that in MM, thrombosis does not drive tumor behavior, and is mostly treatment-related and complicated by other factors such as immobility, and in the absence of additional risk factors, the pro-coagulant state in MM may be counterbalanced by aspirin as efficiently as vitamin K inhibitors and heparin. We speculate that the intravascular nature of MM and other hematopoietic malignancies makes it less likely for them to depend on pro-coagulant factors for disease spread, something clearly of benefit to solid tumor.

Treatment Regimens and Risk of Thrombosis

Similar to patients with solid tumors, VTEs tend to occur within the first three to six cycles of induction in MM, most within the first year from diagnosis or at the time of relapse.¹ As previously mentioned, the risk of venous thrombosis is increased not only in MM, but also possibly in patients with MGUS who are not receiving chemotherapy (two- to threefold increase). This is also the case for arterial thrombosis.^{13,14,18} This baseline risk is further increased by chemotherapy and is dependent on the combination of administered drugs. Single-agent therapy based on either thalidomide or lenalidomide induces thrombosis in a low percentage of individuals (2–4%). This rate is similar to the VTE found in newly diagnosed individuals with solid tumors receiving chemotherapy without prophylaxis (2–4%).^{1,19} VTE incidence greatly increases when thalidomide is used in combination with dexamethasone (12–26%) or multi-agent therapy (16–34%).^{20,21} The risk of thrombosis also

increases when higher versus lower doses of dexamethasone are combined with lenalidomide, as shown in a randomized phase III trial comparing lenalidomide with low (40 mg weekly) versus high (40 mg on days 1–4, 9–12, and 17–20) dose dexamethasone. VTE occurred in 12% of patients treated with low-dose as compared with 26% of those receiving high-dose dexamethasone.²² Interestingly, the higher risk of thrombosis is not limited to thalidomide or lenalidomide-containing regimens. The use of melphalan with prednisone increases VTE (11%), which is not further enhanced upon addition of thalidomide, as shown in a randomized controlled trial.²³ Furthermore, the use of anthracyclins and erythropoietin has also been associated with a higher incidence of VTE.^{24,25}

Protection of Thrombosis by Proteasome Inhibitors

Bortezomib, the first proteasome inhibitor entering into clinical trials, is a highly effective drug for treating MM. Interestingly, its use in different combinatorial therapeutic regimens for either newly diagnosed or relapsed MM protects patients from chemotherapy-induced VTE. A phase III study of thromboprophylaxis by Palumbo *et al.* shows a 1.38 times higher risk of thromboembolism in patients treated with thalidomide without bortezomib.²⁶ In a recent review of data from phase III trials, bortezomib showed a consistent reduction in the risk of thrombosis in both thalidomide- and lenalidomide-containing regimens.²⁷

The mechanism by which this protective effect against thrombosis occurs is still not completely understood. Likewise, this putative protective effect should not be used as the reason to omit thromboprophylaxis in patients receiving IMiDs and dexamethasone at the same time. Proteasome inhibitors have been shown to dampen pro-coagulant abnormalities and inflammation in non-neoplastic diseases. In a murine stroke model, bortezomib reduced secondary arterial thrombosis, inflammatory responses, and blood–brain barrier disruption with a reduction of infarct volume, possibly by promoting endothelial nitric oxide synthase-dependent vascular protection, and reducing NF- κ B-dependent vascular disruption.²⁸ Platelets have been shown to be activated in MM. While bortezomib inhibits *in vitro* platelet aggregation, that effect is only found with ADP-activated platelet rich plasma but not by other agonists.²⁹ In a murine model of anti-phospholipid syndrome (a disease characterized by arterial or venous thrombosis secondary to the pro-coagulant effect of antiphospholipid antibodies), proteasome inhibition down-regulates the NF- κ B signaling pathway. This in turn leads to a dampening of aPLA-induced endothelial cell expression of tissue factor and pro-coagulant phenotype.³⁰ Several proteasome inhibitors are currently under study for treatment of patients with MM. It remains to confirm whether all provide the same level of protective effect from the development of thrombosis.

Prophylaxis: Thrombotic Risk Reduction and Risk of Bleeding

In selected patients and in the absence of a contra-indication, prophylaxis is started at the time of diagnosis and continued until evident VTE risk factors such as prothrombotic chemotherapy or immobility resolve.³¹ The International Myeloma Working Group proposes using risk-adapted strategies for thrombo-prophylaxis based on stratification of the patient's underlying likelihood of VTE using individual, MM, and therapy-related risk factors.²¹ Aspirin, prophylactic dose low-molecular-weight heparin, and low target INR warfarin seem to be as effective in reducing the risk of VTE, except in elderly patients where warfarin may be less effective than low-molecular-weight heparin.¹¹ It is important to remember that the use of any of these drugs will reduce, but will not eliminate the risk of thrombosis completely. Approximately 5–8% of patients still develop thrombosis despite prophylaxis.^{1,11,31} Many published MM studies have excluded patients with high risk of thrombosis or bleeding that have a clear indication or contraindication for anticoagulation. Thus, patients that are known to be at higher risk for thrombosis such as those with history

of prior thrombosis or MM-induced cord compression are usually treated with anticoagulation at therapeutic doses.

MM is also associated with bleeding. The risk of bleeding depends on the baseline patient comorbidities such as recent surgery, platelet counts, and hemostatic abnormalities associated with serum paraproteins. However, the risk of major bleeding using any type of prophylaxis is low (<0.5%).^{11,32,33}

Conclusion

Individuals with MM have a high risk of thrombosis, but this is mainly thought to be secondary to treatment factors and comorbidities leading to inactivity. The pathophysiology and clinical implications of thrombosis in MM differ from solid tumors. Thromboprophylaxis is indicated in all cases where a patient is at high risk of VTE, such as when using treatments with IMiDs and dexamethasone, and should be given and tailored to all patients who are not at high risk of bleeding.

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