Comment on Larocca et al, page 933

When a little aspirin may be enough

Efstathios Kastritis and Meletios A. Dimopoulos  UNIVERSITY OF ATHENS SCHOOL OF MEDICINE

In this issue of Blood, Larocca et al in a large prospective study show that thrombophrophylaxis with low–dose aspirin is very effective in previously untreated multiple myeloma patients with a low thromboembolic risk receiving lenalidomide with low-dose dexamethasone.1

Venous thromboembolism (VTE) is a frequent complication of multiple myeloma (MM). A prothrombotic state has been observed in MM and its precursor monoclonal gammopathy of undetermined significance. The risk of both venous and arterial thrombosis is increased.2 Thalidomide and lenalidomide and recently pomalidomide immunomodulatory drugs (IMiDs) have substantially changed the management of patients with MM. Lenalidomide and pomalidomide lack the neurotoxicity and other CNS complications of thalidomide. However, IMiDs share a common increased risk of VTE and perhaps arterial thromboembolism. The exact mechanism of prothrombotic activity of IMiDs is not clearly understood. However, IMiDs may enhance platelet aggregation and activation, may cause cytokine-mediated activated protein-C resistance, increase the levels of von Willebrand factor and factor VIII,3,4 and may have an effect on the endothelial cells through significant increase in tissue factor activity.5 In addition, genetic factors may predispose to thalidomide–induced VTE.6 Other host factors such as immobilization (because of surgery, bone fractures, spinal cord compression, advanced age), indwelling catheters, and the use of erythropoietin, which all are common in MM patients, further increase the risk of VTE. When IMiDs are combined with chemotherapy, and especially with high-dose dexamethasone, the risk of VTE increases substantially.7,8 This risk is greater in newly diagnosed than in previously treated MM patients perhaps because of higher tumor load in the untreated patients. In newly diagnosed patients treated with lenalidomide with high-dose dexamethasone, rate of VTE were as high as 67%,9 while in patients with relapsed/refractory MM treated with this regimen it was 17%.10 In newly diagnosed patients the addition of aspirin reduced this risk, but still the incidence of VTE remained high, ranging 19% to 26%.8,9 The reduction of the dose of dexamethasone also reduced the risk of VTE, which nevertheless remained as high as 12%.8

Aspirin, which is indicated for the primary and secondary prevention of arterial thrombosis (ie, in coronary and cerebral arteries) may abrogate some of the above effects of IMiDs. Venous thrombi consist mainly of fibrin and red blood cells, and arterial thrombi of platelets and fibrin, but in both the activation of the endothelium, platelets, leukocytes, and high levels of coagulation factors are implicated. Aspirin reduces platelet activation and aggregation and may also regulate COX-1/COX-2 balance and affect the levels of proinflammatory cytokines such as IL-6 or TNF-α, and partially inhibit tissue factor activity.6

The International Myeloma Working Group recommends that factor patients who are treated with IMiDs receive some form of VTE prophylaxis: low-risk patients should receive low-dose aspirin and those at higher risk for VTE should receive either low molecular weight heparin (LMWH) or warfarin with a target International Normalized Ratio of 2–3.11 Two large studies from the same group have been added since the publication of these recommendations. The first study, in patients treated with various thalidomide-based regimens (with or without bortezomib), indicated that aspirin may not be inferior to LMWH and both are probably more efficacious than fixed low-dose warfarin.12

In the present study by Larroca et al1 all patients received lenalidomide with low-dose dexamethasone (Rd) for 4 cycles, followed by cyclophosphamide for stem-cell mobilization and collection before consolidation with either MPR (melphalan, lenalidomide, prednisone) or melphalan 200 mg/m2. Patients were randomized to either low-dose aspirin (100 mg/d) or enoxaparin 40 mg/d at the beginning of the study; prophylaxis was given during the 4 cycles of Rd and while on MPR. The frequency of VTEs in the aspirin group was very low (2.27%), as it was in the enoxaparin group (1.2%). However, all cases of pulmonary embolism occurred in the aspirin group while superficial thrombophlebitis also occurred in a few patients in the aspirin group. As has been previously observed, VTEs occurred early after the initiation of treatment, within a median of 1.3 months.

How does this study improve our strategies for VTE prevention in MM patients who are treated with lenalidomide? One of the strengths of this trial is the randomization of a large number of homogeneously treated patients with very similar risk factors for VTE: all were at low risk for VTE, they had no significant comorbidities, and were eligible for high-dose therapy with an age limit of 65 years or younger (median age of 58 years). In contrast, in previous studies of lenalidomide with dexamethasone,8,9 patients were older (median age around 65 years) including those with 1 or more risk factors for VTE. Furthermore, Larocca et al here provide an opportunity to prospectively identify patients with low-risk features for VTE: relatively young (ie,
younger than 65 years of age), with no co-morbidities such as history of DVT or arterial thromboembolic events, recent orthopedic surgery or verteplasty, immobilation, inherited thrombophilic abnormalities, history of coronary ischemic disease, atrial fibrillation. Nevertheless, the dose of dexamethasone is also a major risk factor and should be considered when deciding on the type of VTE prophylaxis. Thus, based on this study by Larocca et al, in newly diagnosed MM patients treated with lenalidomide and low–dose dexamethasone who are at low risk for VTE, aspirin reduces the risk of VTE to < 3% and may be considered an appropriate form of thromboprophylaxis.

According to the design of the study, the expected incidence of VTE in the aspirin group will be 12% to 67%. However, we must acknowledge that we do not know the real incidence of VTE in young MM patients with no risk factors for VTE who receive lenalidomide with low–dose dexamethasone without any type of prophylaxis. If one had to provide an estimate, one could anticipate that this risk would be well below 10%.

While this study by Larocca et al addresses the issue of prophylaxis in low–risk patients, we still need data from prospective studies to define the optimal thromboprophylaxis regimen for patients treated with lenalidomide–based induction regimens at intermediate or high risk for VTEs or those treated with lenalidomide and high–dose dexamethasone. Based on currently available data, it seems that aspirin may not be adequate for patients at intermediate or high risk and these patients should receive LMWH for at least the initial phase of induction. New antithrombotic agents (thrombin and factor Xa inhibitors) may also be evaluated in this context. Finally, genetic polymorphisms that have been shown to play a role in the development of VTE in patients treated with thalidomide–based regimens may also prove to be of value.

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REFERENCES


Comment on Ubukawa et al, page 1036

Exit strategy: one that works

Narla Mohandas NEW YORK BLOOD CENTER

Enucleation is the culmination of terminal erythroid differentiation. It results in the release of 2 million new enucleate reticulocytes into your circulation and mine each second. In this issue of Blood, Ubukawa and colleagues shed new light on the mechanism, showing that non–muscle myosin IIb is intimately involved.

Mammalian red cells and their immediate precursors, reticulocytes, are, unlike their counterparts in some other vertebrates, devoid of nuclei as a result of an “asymmetric” cell division at the final step of terminal erythroid differentiation. Fission of the erythroblast generates the enucleate reticulocyte and a larger moiety in which an extruded nucleus is encased in a plasma membrane (pyrenocyte). There has over many years been keen interest in defining the molecular machinery responsible for enucleation and in the similarities and differences between this process and classic cytokinesis, which produces 2 identical daughter cells. By studying and comparing both processes, Ubukawa and colleagues offer new insights into the roles of various cytoskeletal proteins in the 2 cases.

Inhibition of non–muscle myosin II ATPase by blebbistatin blocked both cell division and enucleation, implying its participation in both processes and establishing a previously undefined role for myosin in enucleation. Non–muscle myosin IIa and myosin IIb are both

Photomicrographs illustrating the different steps during the enucleation process. The nucleus is first displaced to one side of the erythroblast (left panel). A contractile actin ring is then formed to pinch off the nascent reticulocyte from the nucleus (middle panel). Subsequent redistribution of membrane between the 2 lobes of the dividing cell by vesicle shuttling further restricts the area of contact between the 2 emerging cells (right panel). Images courtesy of Dr Marcel Bessis.
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