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Thromboprophylaxis in multiple myeloma: is the evidence there?

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“...patients with multiple myeloma often have transient risk factors, such as immobilization, infections and surgery, and thromboprophylaxis strategies need to be re-evaluated in these situations.”

The clinical outcome of patients diagnosed with multiple myeloma has improved with the introduction of the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide [1–3]. Simultaneously, a high rate of venous thromboembolism (VTE) has been observed when using these agents, especially in combination with chemotherapy and high-dose corticosteroids and in newly diagnosed patients [1,4–6]. VTE risk is higher at the time of diagnosis than after relapse [7,8]. Treatment with the proteasome inhibitor bortezomib has not been associated with an increased risk of VTE, and when bortezomib is given in combination with thalidomide or lenalidomide the VTE incidence is low, suggesting a protective role of bortezomib on VTE.

Before it became evident that treatment with IMiDs was associated with an increased risk of VTE, investigators did not require the use of any thromboprophylaxis, and VTE was observed in 25–60% of patients with some combinations [9]. This has led to a widespread use of thromboprophylactic measures in these situations. Which agent is optimal for preventing VTE in multiple myeloma is a matter of debate. Expert opinions and clinical guidelines vary in their recommendations, with some suggesting low-molecular-weight heparin (LMWH), warfarin and aspirin, while others recommend against aspirin in any setting [10–13]. Recently published randomized clinical trials on the issue have shed light on this clinical dilemma.

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LMWH as thromboprophylaxis

According to the American College of Chest Physicians (ACCP) guidelines, LMWH (and fondaparinux) are considered the optimal thromboprophylaxis for VTE [13]. Randomized clinical trials have consistently shown this treatment to be superior to placebo in high-risk patients. Compared with unfractionated heparin, there is similar efficacy but lower risk of bleeding [13]. Studies of multiple myeloma patients treated with thalidomide or lenalidomide with LMWH have shown promising results, with a VTE incidence of approximately 3–15% [9]. In newly diagnosed multiple myeloma patients treated with LMWH, the incidence of VTE has varied between 3 and 24%.

There are several advantages with the use of LMWH. The treatment can be given as a fixed weight-adjusted dose once daily, which does not require monitoring. Side effects, such as bleeding, are less common than when using unfractionated heparin or warfarin, and there are fewer drug interactions. Disadvantages include subcutaneous injection, cost and a small risk of heparin-induced thrombocytopenia.

Heparin can accumulate in multiple myeloma patients with impaired renal function. By extrapolating data from other studies, dose adjustment of LMWH is recommended in patients with creatinine clearance below 30 ml/min. For example, enoxaparin can be given at the dose of 30 mg/day instead of 40 mg [9]. In addition, anti-Factor Xa should be monitored closely to minimize risk of overanticoagulation. Furthermore, LMWH has been used without major bleeding risks in patients with thrombocytopenia after stem cell transplantation, and is thus considered an option in that setting [14].

Warfarin as thromboprophylaxis

According to the ACCP guidelines, warfarin is not recommended as thromboprophylaxis in medical patients at risk of VTE [13]. The major advantage of warfarin is that it can be taken orally; however, there is a need for continuous monitoring, and its use is associated with a higher risk of bleeding than other agents. Furthermore, warfarin is usually not recommended in patients with cancer due to drug interactions, risk of bleeding during episodes of thrombocytopenia and a higher risk of complications in patients with liver metastasis [12,13].

“Although aspirin is inferior to low-molecular-weight heparin in preventing venous thromboembolism in general, it does seem to have some protective effects.”

The data on warfarin as thromboprophylaxis in multiple myeloma is also controversial. Some studies have used fixed low-dose warfarin, whereas others have used full dose. Using these approaches, the incidence of VTE has been shown to vary from 8 to 31%, with higher risk among patients treated with a fixed low dose of warfarin [9]. In one study, a similar effect with both strategies was found, but a higher risk of bleeding in patients treated with the full-dose warfarin was noted [15]. In patients with thrombocytopenia, the risk for bleeding is highest among patients treated with full-dose warfarin.

Aspirin as thromboprophylaxis

Aspirin's anti-thrombotic effects are mainly due to reduced platelet aggregation caused by the inhibitory effect of thromboxane A₂. Thus it has primarily been used for preventing arterial thrombosis. Whether it has a place in preventing VTE is a matter of debate. Although aspirin is inferior to LMWH in preventing VTE in general, it does seem to have some protective effects. One study including 17,644 patients undergoing orthopedic surgery showed a significant risk reduction in VTEs compared with placebo [16]. In three out of four randomized studies on patients undergoing orthopedic surgery, there was no difference observed in incidence of VTE between the aspirin group and other anti-thrombotic agents. Furthermore, in a meta-analysis of 135,000 medical patients at high risk of VTE, there was a 25% significant reduction in pulmonary embolism [17]. In recent guidelines, the ACCP recommend against the use of aspirin for any patient group [13]. Conversely, the American Association of Orthopedic Surgeons recommends aspirin as an equal alternative to heparin or warfarin in standard-risk patients undergoing total hip or knee arthroplasty [18]. There is some evidence from before/after studies in multiple myeloma, indicating a protective mechanism for aspirin. Interestingly, some authors have found evidence of platelet aggregation [5] and activation caused by thalidomide, which is also abrogated by aspirin [19]. Furthermore, low-dose aspirin has been shown to be safe in patients with thrombocytopenia [5].

Randomized clinical trials on optimal thromboprophylaxis in multiple myeloma patients

Recently, two very important studies on optimal thromboprophylaxis in multiple myeloma were published. Both are randomized clinical trials including newly diagnosed multiple myeloma patients treated with IMiDs.

In the first prospective, multicenter Phase III trial, Palumbo *et al.* included newly diagnosed multiple myeloma patients that were eligible for autologous transplantation and were treated with either bortezomib, thalidomide (200 mg/day) and dexamethasone (n = 234), or thalidomide and dexamethasone (n = 236), as well as patients not eligible for transplantation that were treated with bortezomib, melphalan, prednisone and thalidomide (n = 189). These patients were randomized to receive aspirin (100 mg/day), warfarin (1.25 mg/day) or enoxaparin (40 mg/day) for the duration of the induction therapy [20]. A total of 43 of the patients (6.5%) experienced a serious thromboembolic event, acute cardiovascular event or sudden death during the first 6 months. There was no significant difference in the incidence of thromboembolic events between the three groups, with an incidence of 3.2, 5.9 and 8.2% in the LMWH, aspirin and warfarin groups, respectively. In elderly patients, warfarin was less effective than LMWH. The incidence of bleeding was not significantly different in the three arms [20].

“Whether aspirin is sufficient in patients with more than one venous thromboembolism risk factor is not currently known.”

The second study included 342 multiple myeloma patients that received four cycles of lenalidomide–dexamethasone as induction and were randomized to either aspirin (100 mg/day) or enoxaparin (40 mg/day) [21]. Based on seven VTE events, the incidence of VTE was

not statistically different between the arms, being 2.3% in the aspirin group and 1.2% in the LMWH group. No major hemorrhagic complications were reported.

Recommendations to prevent VTE in multiple myeloma

In 2008, an expert panel reported on consensus guidelines, which were published before the data from the two randomized clinical trials were available [10]. The panel recommended the use of LMWH in multiple myeloma patients treated with IMiDs with high-dose dexamethasone or doxorubicin, or when more than one risk factor for VTE was present [10]. Aspirin was recommended when one or no other risk factors were present. Additionally, full-dose warfarin was suggested as an alternative to LMWH, despite the lack of corroborating data.

“As many multiple myeloma patients have additional risk factors, low-molecular-weight heparin is the drug of choice in most patients.”

Do these new data from the two published randomized clinical trials change the way we should prevent VTE in multiple myeloma patients treated with IMiDs? Based on the findings from these studies, it can be concluded that aspirin could be an effective and cheaper alternative to LMWH as thromboprophylaxis. There are, however, several issues to take into account when interpreting the results of these studies. First, patients at high risk of thromboembolic events, such as patients with a previous history of VTE, severe cardiac disease, uncontrolled diabetes mellitus, infections, immobilization or surgery were not included. Second, in the first study a majority of the patients were also treated with bortezomib, which is probably associated with a reduced risk of VTE. Third, anthracyclines were not used in any of the studies and, according to the risk model proposed by Palumbo *et al.*, the dose of dexamethasone was not high. The findings from the two published randomized clinical trials thus cannot be generalized to all multiple myeloma patients treated with IMiDs. The results apply to multiple myeloma patients at low or standard risk of VTE. Whether aspirin is sufficient in patients with more than one VTE risk factor is not currently known. However, it is clear that all multiple myeloma patients who do not have excess risk of bleeding and are treated with thalidomide or lenalidomide in combination with dexamethasone or chemotherapy should receive thromboprophylaxis. Still, individual risk-based strategy still needs to be applied. Importantly, patients with multiple myeloma often have transient risk factors, such as immobilization, infections and surgery, and thromboprophylaxis strategies need to be re-evaluated in these situations. As many multiple myeloma patients have additional risk factors [22], LMWH is the drug of choice in most patients. Aspirin should be restricted to patients with no or only one additional risk factor as previously recommended [10].

Summary & future perspectives

Thromboprophylaxis remains a clinical challenge in multiple myeloma. Recently published randomized clinical trials on multiple myeloma patients with low risk of VTE and who are being treated with thalidomide or lenalidomide show that aspirin and LMWH are effective in lowering the VTE risk. No prospective studies are available on patients with more than one

risk factor for VTE. Individual-based risk stratification should be taken into account when choosing the agent.

Future studies on risk factors, thromboembolic strategies and pathogenesis of thrombosis in multiple myeloma will increase our understanding of the hypercoagulable state in plasma cell dyscrasias. Also, there is need to expand our knowledge on orally available thrombin and Factor Xa inhibitors in multiple myeloma [23].

Biography

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