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Commentary Open Access

Multiple Myeloma and Venous Thromboembolism: Where are we at?

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Commentary

Venous thromboembolic events (VTE) in patients with multiple myeloma (MM) remain a frequent occurrence associated with increased mortality [1-3]. Effective and safe thromboprophylaxis is therefore of paramount importance but the optimal antithrombotic regimen has not been established yet and risk-stratification remains an open issue requiring ongoing attention. Residual VTE rates remain high despite enforcement of current available International Myeloma Working group (IMWG) recommendations highlighting their suboptimal nature [4,5]. Additionally, recent studies show that type and dosing of thromboprophylaxis is variable and not accounted for by risk stratification choice [6].

The first step towards minimizing the rates of VTE is to develop an effective and validated risk stratification tool. A number of clinical risk scores have been presented recently. The Myeloma Clot Score (MSC) for the selection of patients likely to benefit from thromboprophylaxis assigns points to previous VTE, low or high dose dexamethasone, presence of central venous catheter, Asian race, use of EPO, BMI, use of thalidomide and whether the patient receives warfarin [7]. The IMPEDE VTE risk score was presented recently by Sanfilippo et al. and identifies three risk groups [8]. Finally, the HAS-RISC score specific for MM patients starting IMiD therapy combines 7 clinical factors into a model that stratifies patients as standard or high risk for VTE [9].

It has been suggested however that to accurately reflect and capture all aspects of the unique procoagulant profile of the myeloma patient VTE risk assessment models must incorporate biomarkers of blood hypercoagulability or endothelial cell activation associated with increased VTE risk in these patients. So far, no group has established a clear link between increased risk of thrombosis and a generic marker of coagulation and consequently no such marker is included in risk assessment proposed by the IMWG. Given the complexity and heterogeneity of the coagulation profile of myeloma patients such a task is to say the least demanding. Ideally a global marker of hemostasis that can be assessed using point of care tests to pinpoint patients with prothrombotic hemostatic profiles or even highlight those with features of resistance to heparin or other anticoagulation needs to be recognized.

It has been demonstrated that in MM patients D-dimer and fibrin monomer levels are increased and thrombin generation is attenuated [10-12]. Our group recently showed that Longer procoagulant phospholipid-dependent clotting time, lower Endogenous thrombin potential (ETP) and higher tissue factor pathway inhibitor (TFPI) concentrations are associated with increased VTE occurrence in patients with newly diagnosed multiple myeloma in the context of the ongoing prospective ROADMAP-MM-CAT Study [13]. At 12 month follow-up cumulative VTE rate was 10.4% despite application of the IMWG guidelines. NDMM patients showed biological signs of endothelial activation and increased cellular and plasma coagulability. Procoagulant phospholipid clotting time (Procoagulant-PPL) was shorter, P-selectin levels lower and thrombin generation attenuated overall compared to healthy subjects. Patients with Procoag-PPL® clotting time ≥ 47s had a 3.5-fold higher risk of VTE as compared to those with a Procoag-PPL® clotting time shorter than this cut-off. We assume that this unexpected finding is in accordance with the lower levels of P-selectin seen in these patients and possibly reflects a status of platelet exhaustion. Patients with ETP ≥ 1087 nMxmin versus patients with ETP<1087 nMxmin had a lower VTE risk. In addition, patients with TFPI ≥ 39 ng/ml versus those with TFPI<39 ng/ml had a 7.75 higher VTE risk (OR=7.74 95% CI (1.51-39.70). These findings support the idea that TFPI levels increase in plasma and that thrombin generation attenuation actually reflects endothelial cell activation rather than down-regulation of plasma hypercoagulable state. Multivariate analysis confirmed that Procoag-PPL® and ETP were independent risk factors for VTE and our group therefore plans to prospectively incorporate these two biomarkers into a RAM for VTE in these patients in combination with clinical and disease specific risk factors.

The second step towards VTE minimization is to determine the most appropriate, safe and effective agent for thromboprophylaxis. IMWG recommendations recommend use of low dose aspirin for low risk patients and administration of low molecular weight heparin (LMWH) or therapeutic dose warfarin for high risk patients. Recommendations are based on data from the limited number of clinical trials that had taken place prior to 2014 when the guidelines were published. Currently, the role of direct oral anticoagulants (DOACs) is being increasingly investigated in cancer associated thrombosis and prophylaxis and in MM patients specifically given their user-friendly route of administration and lack of need for monitoring. None of the DOACs is currently licensed for thrombosis prophylaxis in cancer patients. Carrier et al. demonstrated efficacy and safety of apixaban 2.5 mg twice daily versus placebo to prevent VTE in patients with cancer (VTE in 4.2% of patients in the apixaban group versus 10.2% in the placebo group, hazard ratio 0.41; 95% confidence interval 0.26 to 0.65; $p<0.001$) [14-17]. Results of the CASSINI trial (rivaroxaban for VTE prevention versus placebo in ambulatory high-risk for VTE patients with cancer) were released recently. Rivaroxaban was not found to result in a significantly lower incidence of VTE during the study. More interestingly there is also an ongoing multi-center trial comparing DOACs, LMWH and warfarin for VTE prophylaxis in cancer patients that is in recruitment (CANVAS trial, NCT02744092). Data on the use of DOACs in VTE prophylaxis is missing. RCTs are required to assess their efficacy versus LMWH in high VTE risk patients and versus aspirin in low VTE risk patients and answer the question of which agent to opt for, for which MM patient and for how long?

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An update of the IMWG guidelines on VTE prevention in MM patients is much needed given that despite their application by most MM physicians the residual VTE rates and associated morbidity remains high. Currently there is no robust clinical data on which to base such an update. Efforts are directed in the right direction as the complex interactions between the MM microenvironment and components of plasma and cellular hypercoagulability are being studied and as the role of DOACs is being increasingly investigated in the context of clinical trials.

References

1. Schoen MW, Luo S, Gage B (2018) Association of venous thromboembolism with increased mortality in patients with multiple myeloma. J Clin Oncol 36: 8051-8059.
2. Falanga A, Marchetti M (2009) Venous thromboembolism in the hematologic malignancies. J Clin Oncol 27: 4848-4857.
3. Kristinsson SY, Pfeiffer RM, Bjorkholm M, Goldin LR, Schulman S, et al. (2010) Arterial and venous thrombosis in monoclonal gammopathy of undetermined significance and multiple myeloma: a population-based study. Blood 115: 4991-4998.
4. Palumbo A, Rajkumar SV, Dimopoulos MA, Richardson PG, Miguel SJ, et al. (2008) Prevention of thalidomide and lenalidomide-associated thrombosis in myeloma. Leukemia 22: 414-423.
5. Terpos E, Kleber M, Engelhardt M, Zweegman S, Gay F, et al. (2015) European Myeloma Network guidelines for the management of multiple myeloma-related complications. Haematologica 100: 1254-1266.
6. Bradbury C (2017) Thrombotic events in patients with myeloma treated with immunomodulatory drugs; results of the myeloma xi study in blood. Blood 130: 553.
7. Sanfilippo KM (2018) Prediction of venous thromboembolism (VTE) in multiple myeloma (MM): Myeloma Clot Score (MCS). J Clin Oncol 36: 6585.
8. Sanfilippo KML (2018) Predicting risk of venous thromboembolism in multiple myeloma: The impede VTE score. Blood 1: 1-2.
9. Sanfilippo KML (2018) The HAS-RISC score for Venous Thromboembolism (VTE) risk stratification in newly diagnosed multiple myeloma patients starting Immunomodulatory Drugs (IMID). Blood 1: 1-2.
10. Legendre P, Verstraete E, Martin M, Poinsard A, Perrot A, et al. (2017) Hypocoagulability as assessed by thrombin generation test in newly-diagnosed patients with multiple myeloma. Blood Cells Mol Dis 66: 47-49.
11. Ay C, Dunkler D, Pirker R, Thaler J, Quehenberger P, et al. (2012) High D-dimer levels are associated with poor prognosis in cancer patients. Haematologica 97: 1158-1164.
12. Crowley MP, Eustace JA, O'Shea SI, Gilligan OM (2014) Venous thromboembolism in patients with myeloma: Incidence and risk factors in a "real-world" population. Clin Appl Thromb Hemost 20: 600-606.
13. Fotiou D, Sergentanis TN, Papageorgiou L, Stamatelopoulos K, Gavriatopoulou M, et al. (2018) Longer procoagulant phospholipid-dependent clotting time, lower endogenous thrombin potential and higher tissue factor pathway inhibitor concentrations are associated with increased VTE occurrence in patients with newly diagnosed multiple myeloma: Results of the prospective ROADMAP-MM-CAT study. Blood Cancer J 8: 102.
14. Carrier M, Abou-Nassar K, Mallick R, Tagalakis V, Shivakumar S, et al. (2018) Apixaban to prevent venous thromboembolism in patients with cancer. N Engl J Med 380: 711-719.
15. Leleu X, Rodon P, Hulin C, Daley L, Dauriac C, et al. (2013) MELISSE, a large multicentric observational study to determine risk factors of venous thromboembolism in patients with multiple myeloma treated with immunomodulatory drugs. Thromb Haemost 110: 844-851.
16. Park YPP, Jia X (2018) Clinical outcomes with direct oral anticoagulants compared to low molecular weight heparins in the treatment of cancer-associated venous thromboembolism. Blood 1: 1-2.
17. Raskob GE, Van Es N, Verhamme P, Carrier M, Di Nisio M, et al. (2018) Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 378: 615-624.