increase in DNA methylation in the blood, is also surprising. These 3 patients, together with patients presenting haploinsufficiency for TET2, provide fascinating opportunities to study DNA methylation, particularly for 5hmC, in humans. Studies of the transcriptomes of different cell lineages from these patients will undoubtedly provide insight into methylation-dependent gene regulation. Stremenova Spegarova et al have already differentiated hematopoietic lineages from the patients' induced pluripotent stem cells and have shown this differentiation to be correlated with DNA hypermethylation. More detailed studies of these cells might also reveal the genomic distribution of 5hmC, related gene activity, and their influence on hematopoietic lineages. They might also differentiate the function of TET2 from those of TET1 and TET3 while also identifying TET2-specific targets and TET2-dependent tissues. It is reasonable to expect that, in the near future, following the identification of a larger number of patients, studies of TET2 deficiency will reveal a number of new DNA methylation targets and important cellular functions associated with them.

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THROMBOSIS AND HEMOSTASIS

Comment on Bradbury et al, page 1091

Thrombosis in the modern era of multiple myeloma

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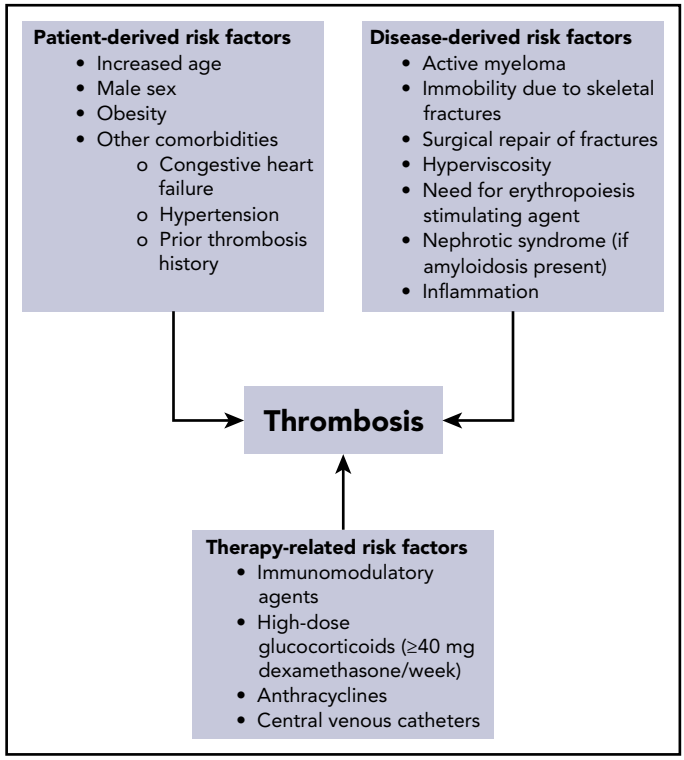
In this issue of *Blood*, Bradbury et al report on behalf of the United Kingdom Medical Research Council (MRC), the results of a pooled, secondary analysis of thrombotic events in the Myeloma IX and XI trials, which tested immunomodulatory agents (IMiDs; thalidomide and lenalidomide) as treatments for newly diagnosed multiple myeloma (MM). The authors found that thrombosis was common, but generally not associated with inferior longer-term outcomes such as overall survival.[1]

This study is the latest chapter in the long story of thrombosis in MM, and examining the broader context is instructive. Myeloma IX and XI collectively constitute some of the largest interventional studies completed in MM; follow-up of subjects is long, and both stem cell transplant candidates and noncandidates were eligible. Prior publications regarding these trials have informed myriad other dimensions of MM management, such as chemotherapy selection and the use of both bisphosphonates and transplantation. MRC investigators deserve substantial kudos for trial design; these studies are an elegant model of trial efficiency, wherein each individual study sheds light on not one, but many areas of clinical equipoise.

Although illuminating, the generalizability today of the study currently under discussion is somewhat limited by the obsolescence of the regimens tested. Almost all of the arms on these trials incorporated "high-dose dexamethasone," or repeated 4-day courses of dexamethasone 20 to 40 mg daily followed by a break. "Low-dose dexamethasone," meaning 20 to 40 mg roughly once weekly, has arguably supplanted high-dose dexamethasone as standard of care since Rajkumar et al published a classic clinical example of "less is more" in MM over a decade ago, namely a randomized study in which high-dose dexamethasone induced higher response rates than low dose, but also more thromboses and worse overall survival.[2] Bradbury et al's data regarding the cytotoxic (ie, IMiD-lacking) regimens are of similarly limited contemporary relevance. These comments are meant not to criticize the selection of regimens used on Myeloma IX and XI, but simply to reflect on the challenge of applying mature clinical trial data within the rapidly evolving landscape of MM therapeutics.

Despite that caveat, the authors substantiate a number of known findings and add vital new ones:

1. Clots are common in MM. The high incident rate of thrombosis observed by Bradbury et al is far higher than that seen in the general population and fits with other studies showing the same.[3] The pathophysiological interplay between thrombosis and MM is complex and incompletely understood, but in many patients multiple risk factors for thrombosis can be identified and even trichotomized for conceptual purposes (see figure). Reflecting upon the individual



Potential factors contributing to increased risk of thrombosis in MM.

components of the classic triad described by Virchow himself and others >150 years ago, namely stasis, endothelial damage, and hypercoagulability, one quickly recognizes why thrombosis disproportionately plagues patients with MM. Few other diseases complete Virchow's triad so thoroughly.

2. Prompting clinicians to consider thromboprophylaxis reduces clots. The International Myeloma Working Group published guidelines in 2008 for comprehensively evaluating thrombosis risk in MM patients receiving IMiDs. Explicit in the guidelines was that the threat in MM was substantial, and all patients warrant prophylaxis, thereby framing the question as "not if, but with what?"[4] Myeloma IX was conducted largely before the guidelines were published, and no thromboprophylaxis recommendations were provided, whereas Myeloma XI came after the guidelines, and prophylaxis was recommended on study, resulting in an ~60% absolute increase in thromboprophylaxis usage from Myeloma IX to XI. As real-world utilization of thromboprophylaxis has been shown to be much lower,[5] it is encouraging indeed to witness that prompting clinicians to consider thromboprophylaxis had a marked effect. Furthermore, the lower thrombosis rate among subjects receiving the same thalidomide-based regimen on Myeloma XI vs IX demonstrated that prompting clinicians not only bolsters thromboprophylaxis implementation but also can actually improve outcomes.
3. Lenalidomide and thalidomide confer similar thrombotic risk. This paper adds the largest body of prospective evidence to date and corroborates existing retrospective data.[6]

How does one apply these data moving forward? As always, uncertainty remains. First, high-dose dexamethasone is now far less commonly employed, ameliorating a significant thrombosis risk factor present in Myeloma IX and XI. Second, proteasome inhibitors, widely used today in MM, but not included with first treatment in Myeloma IX or XI, likely affect thrombosis. Bortezomib may reduce thrombotic risk,[7] whereas carfilzomib perturbs the vascular endothelium and has been associated with increased cardiovascular events, including cardiac ischemia, and so perhaps thrombosis.[8] Incorporating these and other considerations into clinical decision making today is challenging, but published risk stratification models provide an initial roadmap for navigating the issue.[5]

We offer 2 simple take-home messages. (A) Consistent implementation of thromboprophylaxis is vital. The first step in preventing clots is trying to do so. (B) We must improve available strategies. Until recently, the 2 most available agents beyond aspirin required either regular monitoring and had a narrow therapeutic window (warfarin) or involved frequent subcutaneous injections (low-molecular-weight heparins). Whether the still >10% thrombosis incidence on Myeloma XI was due to poor adherence to these cumbersome approaches, true pharmacological failure, or other causes is unknown, but whatever the cause, that still excessive event rate illustrates that more consistently administering prophylaxis can only partially meet the need. Developing more practical and efficacious options is also required. Fortunately, novel agents such as direct oral anticoagulants hold tremendous promise in this space and already have proven efficacy and safety in patients with primarily solid tumors.[9] Most definitive thromboprophylaxis studies to date have included few patients with hematological malignancies, and as such, these drugs are relatively understudied in MM so far. That said, initial investigations via single-arm pilot studies with apixaban prophylaxis in MM patients receiving IMiDs, for instance, have demonstrated low thrombosis rates and minimal bleeding.[10] Larger studies are needed to reveal whether these agents will prove themselves to be the definitive answer. As the research evolves further, Bradbury et al compellingly remind us of the extent of the thrombosis problem in MM and why we should redouble our efforts to mitigate it.

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