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# Significant risk of venous thromboembolism associated with targeted anti-myeloma immunomodulatory drugs. Comment on: Targeted anti-cancer agents and risk of venous thromboembolism

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**Significant risk of venous thromboembolism associated with targeted anti-myeloma immunomodulatory drugs. Comment on: Targeted anti-cancer agents and risk of venous thromboembolism.**

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In their recent publication, Verso et al. provide a timely and important discussion on the evolving risk of venous thromboembolism (VTE) associated with targeted anti-cancer therapies.[1] Building on their review, is it important to consider immunomodulatory drugs (IMiDs) as a critical class of targeted anti-cancer agents with a well-documented increased risk of VTE.[2] IMiDs are a cornerstone of modern multiple myeloma (MM) therapy, with thalidomide, lenalidomide, and pomalidomide approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). Patients with MM, the second most common haematological malignancy, have an eight-fold increased risk of VTE.[3] As with most cancer-associated thrombosis, this increased risk is multi-factorial, encompassing disease-, patient-, and treatment-related parameters. However, within the MM patient population, IMiD therapy is associated with a significantly higher VTE risk, particularly when used in combination with dexamethasone.[4] Importantly, this risk persists despite current thromboprophylaxis strategies, underscoring the need for further evaluation, through dedicated trials and real-world evidence.[5,6]

IMiDs exert their targeted anti-myeloma effects through cereblon (CRBN) E3 ligase binding, which facilitates the degradation of two key B cell transcription factors, Ikaros (IKZF1) and Aiolos (IKZF3).[7] This degradation suppresses the expression of IRF4 and MYC, crucial for the survival of MM cells. Additional anti-MM activity includes the modulation of adhesion molecules like TNFα, immunomodulatory, and anti-angiogenic effects.[8] The precise mechanisms underpinning the pro-thrombotic potential of IMiDs have yet to be fully characterised. However, evidence suggests that these agents increase the expression of tissue factor and vascular endothelial growth factor, reduce thrombospondin levels, and contribute to cytokine-mediated resistance to activated protein C.[9] Furthermore, thalidomide therapy has been associated with an upregulation in von Willebrand factor and Factor VIII levels.[10] Interestingly, there is also evidence to suggest that individual genetic variation, based on a set of single nucleotide polymorphisms (SNPs) in genes associated with inflammatory response, DNA damage repair, and endothelial activation, may predispose patients to IMiD-associated VTE.[11]

Following recognition of the elevated VTE risk associated with IMiD therapy, the International Myeloma Working Group (IMWG) published thromboprophylaxis practice guidelines in 2008, recommending aspirin for low-risk patients and low-molecular-weight heparin (LMWH) for high-risk patients.[12] However, clinical trial data provide strong evidence of the persistent increased VTE risk associated with IMiD-based regimens in MM. Analysis from the randomised phase II GRIFFIN trial demonstrated an overall VTE rate of 12.9% in patients receiving lenalidomide as part of their treatment regimen.[5] Of these patients, 65.4% had received anti-thrombotic prophylaxis, which was aligned to the International Myeloma Working Group (IMWG) recommendations. Similar findings were observed in the Myeloma XI trial, which enrolled 4,358 newly diagnosed MM (NDMM) patients treated with thalidomide- or lenalidomide-containing regimens.[6] The VTE incidence rate in this trial ranged from 10.7% to 13.2%, depending on the specific regimen, despite 80.5% of patients receiving thromboprophylaxis prior to their VTE events. More recently, a study involving 672

NDMM patients on lenalidomide-based induction regimens found that 12% experienced VTE within the first year of treatment.[13] These findings illustrate that, despite adherence to current thromboprophylaxis guidelines, a substantial risk of VTE persists in MM patients receiving IMiDs, underscoring the need for discussion of this important topic and evaluation of current guidelines. The emergence of novel anti-MM regimens has further complicated VTE risk stratification, and the role of newer agents like direct oral anticoagulants (DOACs) in MM primary prophylaxis remains uncertain.

In conclusion, IMiDs are an important class of targeted anti-cancer drugs associated with a well-documented increased risk of VTE in MM. However, despite recent Intergroupe Francophone du Myélome (IFM) recommendations that favour LMWH or DOACs instead of aspirin for all patients receiving IMiD-dexamethasone therapy, there remains a lack of international consensus regarding optimal thromboprophylaxis.[14] Furthermore, the use of newer VTE risk stratification tools which incorporate IMiD therapy, such as the SAVED, IMPEDE, and PRISM models, have yet to be widely adopted.[15] Thus, further research, incorporating real-world evidence and comparative analyses of anticoagulant strategies, is urgently needed to develop updated international guidelines and reduce the risk of VTE in MM patients receiving IMiDs.

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