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EDITORIAL COMMENT

The Rise and Fall of C-Reactive Protein

Can it Predict Immune Checkpoint Inhibitor–Associated Venous Thromboembolism?

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Venous thromboembolism (VTE) is a major complication in patients with active cancer and/or receiving cancer therapies. Studies have shown that as many as 1 in 5 patients with cancer develop VTE.[1] VTE can lead to hospitalizations, a delay or change in cancer treatments, impact on quality of life, and other complications such as bleeding and recurrent thrombosis.[2] Therefore, identifying patients at high risk of VTE and implementing effective VTE prevention strategies are crucial and can lead to improvement in patient outcomes.

The oncology field continues to advance quickly, with many new therapy options constantly expanding the treatment landscape. However, although new therapies lead to improvements in disease control and survival, they can also be associated with an increased risk for complications such as VTE. Immune checkpoint inhibitors (ICI) are one such example. Since their introduction in 2011, ICIs have revolutionized the treatment landscape and have become an integral part of treatment regimens for a variety of cancers. As of January 2024, 11 ICIs had been approved by the U.S. Food and Drug Administration with 43 distinct indications in at least 20 cancers.[3] As a result, the proportion of patients who are eligible for ICIs rapidly increased from 1.5% in 2011 to 43.6% in 2018.[4,5] With the increasing use of ICIs, there are rising concerns of increased risks for arterial and venous thrombosis associated with their use.[6] Although data remain mixed as to whether ICIs truly increase the risk for thrombosis compared with traditional chemotherapy, current evidence indicates that the risks are not negligible, and this complication should not be overlooked.[7,8] How to best identify patients receiving ICIs at risk for VTE remains elusive, as the most validated VTE risk prediction model, the Khorana score,[9] was developed before the ICI era, and its applicability to patients on ICIs has not been consistent.[6,8] Therefore, the identification of novel risk factors or the development of dedicated risk prediction models is needed in the ICI-treated population. C-reactive protein (CRP) is a widely available inflammatory biomarker, and CRP dynamics (changes in CRP) during ICI treatment were previously shown to correlate with disease responses and progression-free and overall survival.[10,11] As a growing body of evidence on thromboinflammation indicates that inflammation could be a main driver of VTE,[12] the link between CRP and VTE occurrence in this population is of great interest.

In a retrospective cohort study reported in this issue of *JACC: CardioOncology*, Moik et al[13] investigated the association between the risk for VTE and CRP dynamics within the first 3 months after initiating ICIs. Patients from 2 Austrian academic centers were included: 405 in the derivation cohort and 417 in the external validation cohort. The primary endpoint was VTE (including deep vein thrombosis, pulmonary embolism, and VTE at unusual sites such as splanchnic or cerebral vein thrombosis) during ICI therapy, and secondary endpoints included disease progression and all-cause mortality. A CRP rise was defined as a ≥2-fold increase in CRP level compared with baseline within 3 months of ICI initiation, while a CRP decline was defined as a ≥50% decrease in levels. The cumulative incidence of VTE in the entire cohort was 12.7% (95% CI: 6.9%-20.5%) over a median follow-up period of 7.9 months. A CRP rise was found

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to be associated with a 2- to 3-fold increased risk for VTE compared with no CRP rise (subdistribution HR: 2.34; 95% CI: 1.12-4.91) using death as a competing risk, while a CRP decline was associated with a nonsignificant reduction in the risk for VTE. The results remained consistent after adjusting for multiple confounders, including age, sex, cancer type, stage, Eastern Cooperative Oncology Group performance status, comorbidities, disease progression, and baseline CRP level. The investigators further supported the results through additional analyses including applying CRP rise as a time-dependent covariate and external validation. A sensitivity analysis by excluding the 17% of patients on anticoagulation showed that the effects of a CRP rise on VTE occurrence was even more profound, with a subdistribution HR of 4.57 (95% CI: 1.43-14.59).

This is the first study in the literature to demonstrate the association between CRP dynamics and VTE risks specifically in patients with cancer receiving ICIs. The positive association between a CRP rise and VTE reinforces the purported role of inflammation on VTE in this population. Although further validation is needed, it is exciting to find that a commonly used and widely available biomarker could be used for VTE risk stratification. In both derivation and validation cohorts in the present study, the 6-month cumulative incidence of VTE in those with CRP rise was 9% to 10%, on par with patients with Khorana scores ≥2, for whom thromboprophylaxis is suggested by current international guidelines.[14,15] Therefore, with further validation, follow-up studies may investigate whether thromboprophylaxis could be beneficial, particularly in patients with early CRP rise treated with ICI therapy. CRP dynamics also take into account the time-varying factor after the start of ICIs, which is unique from most currently available biomarkers or risk prediction models that assess risk only at the start of therapies (1 static time point). However, the need for more than 1 assessment for risk stratification (instead of up-front risk determination) may increase complexity and delay identification of high-risk patients and the timely implementation of effective prevention strategies such as thromboprophylaxis. Therefore, further studies, preferably prospective, are needed to determine the optimal timing, risk assessment, and implementation of effective prevention strategies.

This study by Moik et al[13] provides important data to deepen our understanding of the mechanisms of ICI-related VTE as well as to provide a novel risk stratification strategy. More work is needed, but the future is bright! We have much to anticipate on the development of more practical tools to identify high-risk patients efficiently and to apply prevention strategies effectively and safely.

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