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EDITORIAL COMMENT

The Value of Performance Status in Predicting Clinical Outcomes in Patients With Cancer-Associated Pulmonary Embolism*

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The occurrence of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is commonly associated with a cancer diagnosis. Specifically, 20% to 30% of all initial VTE events occur in oncological populations, with 5% to 20% of patients developing VTE following a cancer diagnosis.[1,2] The relatively high incidence of VTE in patients with cancer is attributed to disease- and treatment-related factors,[1] described in Virchow's triad, including stasis of blood flow, endothelial injury, and a state of hypercoagulation.[3]

Current guidelines for the treatment and secondary prevention of VTE during cancer treatment recommend long-term anticoagulation.[2] The initial treatment phase is normally 3 to 6 months. After the initial treatment phase, ongoing coagulation is indicated for secondary prevention but careful, ongoing re-evaluation of potential risks, such as clotting and bleeding, is essential. Low-molecular-weight heparin (LMWH) was the standard of care because it was found to be more effective than vitamin K antagonists in preventing recurrent VTE.[4] Nonetheless, the economic and patient burden associated with LMWH led to examining the utility of direct oral anticoagulants (DOACs) as a more cost-effective and efficacious strategy for preventing VTE in oncology.[5]

The Hokusai VTE Cancer (Cancer Venous Thromboembolism) study was a landmark randomized, noninferiority trial that compared the efficacy of the DOAC edoxaban against the subcutaneous LMWH dalteparin in preventing recurrent VTE or major bleeding (composite primary outcome) within 12 months in patients with cancer and an acute VTE.[6] Of the 1,046 participants, 12.8% in the edoxaban group experienced the composite outcome compared with 13.5% in the dalteparin group, suggesting that edoxaban was noninferior to dalteparin for the composite outcome (HR: 0.97; 95% CI: 0.70 to 1.36; $P = 0.006$).[6] Fewer participants (7.9%) in the edoxaban group experienced a recurrent VTE compared with 11.3% of participants receiving dalteparin (difference in risk −3.4%; 95% CI: −7.0% to 0.2%).[6] However, major bleeding occurred in 6.9% of participants receiving edoxaban compared with 4.0% of participants in the dalteparin group (difference in risk 2.9%; 95% CI: 0.1% to 5.6%).[6] Importantly, the median treatment duration was longer with edoxaban (median 211 vs 184 days; $P = 0.01$).

Current tools for predicting VTE-related outcomes in cancer are imperfect and do not account for non-cancer treatment-related patient factors, such as performance status (PS), which has been shown to independently predict mortality in patients with cancer-associated pulmonary PE.[7] The study by Farmakis et al[8] in this issue of *JACC: CardioOncology* is a subanalysis of the original Hokusai VTE Cancer study that sheds light on the impact of PS, measured by the Eastern Cooperative Oncology Group (ECOG) scale, on VTE outcomes. The investigators examined whether ECOG PS score at baseline or over follow-up

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visits was associated with anticoagulation discontinuation and the composite outcome of VTE recurrence or major bleeding in patients with cancer-associated PE receiving edoxaban or dalteparin over 12 months.[8] For the purposes of this subanalysis, only patients with a history of PE were included. Compared with baseline, ECOG PS scores declined in 49.4%, were steady in 31.2%, and improved in 19.5% of the cohort. Worse ECOG PS at baseline (HR: 1.46; 95% CI: 1.06-1.99) or during follow-up (HR: 1.59; 95% CI: 1.31-1.93) was associated with a higher risk of anticoagulation discontinuation. Additionally, participants with higher ECOG PS scores were more likely to discontinue edoxaban than dalteparin. Worse ECOG PS during follow-up, but not at baseline, was associated with a higher risk of VTE recurrence or major bleeding combined (HR: 2.13; 95% CI: 1.24-3.67).[8] The investigators concluded that ECOG PS is a valuable indicator of VTE outcomes in patients with cancer-associated PE and may be used to aid treatment decisions regarding anticoagulation.[8]

Two important strengths of this subanalysis involve the integration of ECOG PS as a prognosticator of VTE outcomes in oncology and the inclusion of baseline and time-dependent ECOG PS in the analysis.[8] However, several limitations should be noted. First, although the investigators recognize that exclusion of patients with DVT reduced the sample size, no clear explanation was provided for this decision. Second, the lack of treatment type as a covariate from the multivariable analyses is an important limitation, given that different cancer therapies differentially may alter the risk of VTE recurrence and risk of bleeding.[9] For example, chemotherapy causes damage to the endothelium and increases procoagulant activity.[10]

This subanalysis provides an opportunity to raise a number of additional important points. First, cancer progression accounted for 89% of deaths, whereas only 2.3% of deaths were attributed to VTE. As the investigators stated, patients with deteriorating ECOG PS were more likely to die. A worsening ECOG PS may signal the need to discuss the transition from active treatment to palliative care. Late discontinuation of active treatment near the end of life is associated with worse experiences for patients and caregivers.

Second, patients with worse ECOG PS scores at baseline and during follow-up had a significantly higher risk of discontinuing anticoagulation. Despite limited evidence on continued anticoagulation, long-term anticoagulation is recommended during active cancer treatment[2] with clinical and patient-related factors, such as risk of major bleeding, poor renal function, thrombocytopenia, and patient preferences determining the type and extent of anticoagulation treatment. Notably, patients with poor ECOG PS on edoxaban exhibited a higher risk of terminating anticoagulation therapy compared with those on dalteparin. Plausible explanations for these findings may involve the higher risk of bleeding with DOACs compared with LWMH or concerns related to drug absorption, clinician comfort with LMWH in higher risk patients, or patient preferences.

Interestingly, 125 patients (19.5%) had improved ECOG PS at the end of follow-up as compared with baseline. Poor PS can sometimes be modifiable, and therefore, supportive care strategies such as exercise or rehabilitation programs may be considered for oncology patients on active treatment who have a history of VTE, particularly if they experience functional decline in the absence of disease progression. Although this subanalysis did not establish causation between ECOG PS and the composite outcome, it is hypothesized that better PS may decrease the risk of VTE recurrence and major bleeding.

Several clinical implications can be derived from this subanalysis. In patients with cancer-related VTE and worsening ECOG PS, consideration of overall goals of care (eg, early palliative care/hospice), as well as assessment of possible improvement in PS (eg, rehabilitation/supportive care strategies) are important. Worsening ECOG PS provides a window of opportunity for clinicians to re-evaluate the risks and benefits of active cancer treatment and decide whether transition to palliative care aligns with the patient's goals and preferences. Additionally, regardless of treatment intent, clinicians should assess the patient's ability to participate in supportive care strategies aimed at reversing functional decline.

Future studies should compare alternate metrics of PS as predictors for clinical outcomes in patients with a history of VTE, including those with DVT, and should adjust for treatment type in multivariable analyses. It is also important to examine the performance of frailty as a metric in predicting clinical outcomes and mortality in patients with cancer who have a history of VTE. ECOG PS is associated with frailty, and frailty has been shown to be a superior predictor of mortality and other clinically relevant outcomes in older adults with cancer.[11] Future research should also include more very old patients (age 85+ years), because they are at higher risk of poor PS, bleeding complications, and noncancer mortality, yet are frequently excluded from clinical trials.

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