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IM - EDITORIAL

Targeted prophylaxis in cancer: the evidence accumulates

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The association of cancer and hypercoagulability has been known for at least a century, but it is now increasingly clear that not all cancer patients are equally at risk for thrombotic events. The magnitude of risk varies widely by clinical risk factors such as type of malignancy, comorbid conditions, the clinical setting and therapeutic interventions. A post-menopausal woman with breast cancer receiving adjuvant endocrine therapy may have a very low-risk of venous thromboembolism (VTE). In a meta-analysis of trials with a median follow-up time ranging from 51 to 100 months, rates of VTE range from 2 to 2.8 % with evidence of a protective effect for aromatase inhibitors (absolute risk difference -1.3 % vs. tamoxifen) [1]. In contrast, a patient with metastatic bladder cancer receiving cisplatin may have a very high-risk of VTE. In a retrospective cohort study of primarily solid tumor patients treated in 2008 with cisplatin-based chemotherapy, 18.1 % of patients developed thromboembolic events [2]. There is no doubt that VTE in cancer is consequential: it is the second leading cause of death, associated with short-term and long-term mortality, morbidity, with requirement for long-term anticoagulation with high-risk of bleeding and healthcare resource utilization. Thus, it is important to select high-risk patients for studies of thromboprophylaxis, and it is equally important to *exclude* low-risk patients where the magnitude of benefit is likely to be low.

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Patient selection and risk assessment are therefore crucial to optimize benefit for outpatient thromboprophylaxis in cancer. Several randomized studies have recently been published or presented. Although all have appropriately focused on cancer outpatients receiving chemotherapy, there are important differences in the types of patients included.

In one corner are what might be called "generalist" studies: these include the two largest studies—PROTECHT which used nadroparin, a low-molecular-weight heparin (LMWH) as the prophylactic agent [3], and SAVE-ONCO, which used semuloparin, an ultra-LMWH [4]. Both studies included heterogeneous populations varying by the site of cancer, stage and chemotherapy. Both showed a significant reduction in VTE, but event rates were low (Fig. 1). Hence, study results have not been adopted into clinical practice.

In the opposite corner are what might be termed "niche" studies: these trials are smaller, have focused on very high-risk sites of cancer such as pancreas or myeloma, populations that are homogenous and have high rates of VTE [5]. For instance, in the FRAGEM study of dalteparin thromboprophlyaxis in advanced pancreatic cancer, VTE during treatment (<100 days from randomization) was reduced from 23 to 3.4 % ($p = 0.002$), an 85 % risk reduction [5]. Such findings have led to "soft" recommendations for outpatient prophylaxis in high-risk patients. A criticism of these "niche" studies has been that the findings are applicabe only to a small percentage of cancer patients, and the impact on the public health burden of cancer-associated VTE is low.

Is there a way to marry these two approaches to risk assessment? Can prophylaxis be targeted to high-risk patients and excluded for low-risk patients? In 2008, my colleagues and I developed and validated a risk score that includes five simple variables (Table 1) [6]. This model

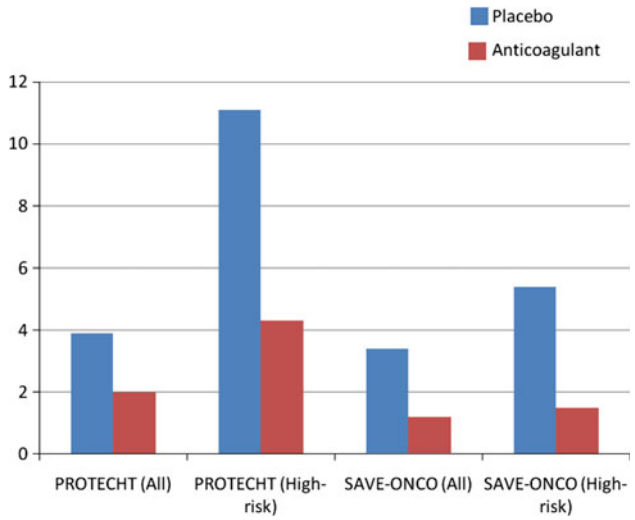

Fig. 1 Rates of VTE in the placebo and anticoagulant arms of the full populations of the PROTECHT and SAVE-ONCO studies as well as the high-risk subgroups (score ≥ 3, based on the risk score by Khorana et al.)

Table 1 Predictive Model for chemotherapy-associated VTE [6]

Patient characteristics	Risk score
Site of cancer	
Very high-risk (stomach, pancreas)	2
High-risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count 350,000/mm^3 or more	1
Hemoglobin level less than 10 g/dl or use of red cell growth factors	1
Prechemotherapy leukocyte count more than 11,000/mm^3	1
Body mass index 35 kg/m^2 or more	1

High-risk score ≥ 3

Intermediate-risk score = 1–2

Low-risk score = 0

was subsequently externally validated in multiple studies. It meets criteria for a level 1 clinical decision rule, and has been endorsed by various guidelines. Nevertheless, can this score be utilized to predict benefit of thromboprophylaxis in high-risk cancer patients?

It is in this context that the paper by Verso and colleagues assumes great importance [7]. The authors present a post hoc subgroup analysis of 1,150 patients enrolled on the PROTECHT study, separated by risk category. Recall that the rate of VTE in the placebo arm of this study was 3.9 % and in the nadroparin arm was 2 %; the number needed to treat (NNT) was 50. When Verso and colleagues re-analyzed the data according to the risk score discussed above, approximately 12 % of the population was defined as high risk. Among these patients, rates of VTE were 11.1 % in the placebo arm and 4.5 % in the nadroparin arm and the NNT fell precipitously to 15. Although specific bleeding rates were not provided, the authors report no differences according to VTE risk. There are three important takeaways from this report: first, the risk score is yet again found to be valid in identifying high-risk patients; second, the clinical benefit to high-risk patients is substantial, and accrues without a concomitant increase in risk of bleeding; and third, the benefit to low-risk patients is quite minimal (NNT = 77), and thus these patients can reasonably be excluded from discussions of prophylaxis.

Additional support to this risk score-based targeted approach comes from a protocol-specified subgroup analysis of the other large "generalist" study. When the risk score is applied to SAVE-ONCO, risk reduction is greater in high-risk patients: 5.4 % in the placebo arm vs. 1.4 % in the semuloparin arm, for score ≥ 3 (HR 0.27) compared to 1.3 vs. 1 %, respectively, for score = 0 (HR 0.71). There are no significant differences in bleeding rates between high- and low-risk populations. These data again suggest that targeted prophylaxis works: the benefit to low-risk patients is minimal while the benefit to high-risk patients is substantial and unaccompanied by an increase in bleeding events. High-risk patients defined by the risk score are currently the subject of a prospective randomized study sponsored by the NIH.

Verso and colleagues also propose a modification of the original risk score by adding points to the score for platinum-based or gemcitabine chemotherapy. Unfortunately, this modification is based on extrapolation from the literature, and is not derived rigorously from a cohort study. The association of cisplatin or gemcitabine with VTE is further complicated by the fact that these agents are primarily used in lung, pancreas and bladder cancers that by themselves are associated with VTE. What portion of the risk can be attributed to the site of cancer, and what portion to chemotherapy can only be judged in large cohort studies using analyses adjusting for these co-variates. A second limitation of the proposed modification is its performance in this limited dataset: the modified score appears to stratify patients well in the placebo arm (8.1 % for high-risk vs. 2 % for low/intermediate-risk combined, $N = 378$), but not in the nadroparin arm (2.2 vs. 1.9 % in high-risk vs. low/intermediate-risk, $N = 765$). Finally, although the performance of the modified score was not rigorously tested (C statistic, sensitivity, specificity and other measures are not provided in this brief report), since its clinical performance seems to be not significantly better (NNT = 17 for high-risk patients vs. 15 for the original score). At this point, the modification can only be considered exploratory, and additional large cohort studies are necessary to identify whether a modified score adds substantially to the predictive power of the original score. In my opinion, a

modification of the original score is necessary to better discriminate among intermediate-risk patients who form approximately 60 % of patients in most of the cohort studies; some of these patients are likely to be in high-risk, and could benefit from prophylaxis. Perhaps emerging biomarkers may provide additional discriminatory power.

It is important to pause and take note of what has been achieved in the field of cancer-associated thrombosis in the past decade. Multiple randomized studies show that outpatient prophylaxis is effective, safe and feasible; a validated risk score helps to identify truly high-risk patients. This paper by Verso and colleagues highlights the potential for clear benefit to patients from thromboprophylaxis. The true measure of success will be met when the findings of investigators can finally help reduce the burden and consequences of thrombotic events for patients with malignancy.

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