Opinion Article

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Anticoagulation and Cancer-Associated Venous Thromboembolism in Ambulatory Patients-Are Factor Xa Inhibitors the Next Logical Step?

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Opinion

Venous Thromboembolism (VTE) is the second leading cause of death in ambulatory cancer patients [1,2]. Cancer patients have an approximate 4-fold greater risk of developing VTE when compared to patients without cancer. The use of chemotherapy in these patients increases VTE risk to approximately 6.5-fold [1]. Roughly 20% of all VTE cases occurring in patients with cancer are primarily within the outpatient setting [2,3]. The 1-year survival rate is approximately one-third the survival rate in cancer patients without a VTE [4]. Because VTE complicates the course of cancer, thromboprophylaxis in this population could reduce the burden of VTE, and potentially lead to improved health outcomes [4]. However the risk of bleeding associated with thromboprophylaxis is higher in cancer patients than among the general population and current thromboprophylaxis guidelines reflect this concern, reserving it for those patients with the greatest risk for a VTE [4].

How do we identify these patients? Current guidelines identify and classify risk factors for cancer-associated thrombosis as either patient-related, cancer-related, or treatment-related [1,3]. Individual characteristics that range from age (patient-related) to the primary site of cancer (cancer-related) to active chemotherapy (treatment-related) have been associated with a risk of VTE [1], however, a patient's overall risk depends on a combination of these risk factors [2]. In an effort to identify high-risk patients that could be eligible for thromboprophylaxis, a risk stratification tool was developed by Alok Khorana and colleagues. This Khorana Risk Score [5,6] scoring system is the only validated risk assessment tool available for the prediction of cancer-associated VTE in outpatients recommended by clinical guidelines, including those of the American Society of Clinical Oncology [2].

The Khorana Risk Score assigns a numerical value of 1 or 2 to patient characteristics that include: Site of Cancer (stomach, pancreas, lung etc.), Laboratory values (Platelet, Leukocyte, hemoglobin) and Body Mass Index. The calculated score ranges from 0 to 7, where the higher the score, the higher the risk of VTE [4].In a prospective observational study of 2700 patients with cancer, Khorana and colleagues found the incidence of VTE was 0.3% among low-risk patients (total score of 0), 2.0% among intermediate-risk patients (a score of 1-2), and 6.7% among high-risk patients (a score of 3 or higher) over a median of 2.5 months [4].

Non-Vitamin K antagonist Oral Anticoagulants (NOACs) have demonstrated effectiveness in both VTE prophylaxis (in patients undergoing major orthopedic surgery) and treatment (in patients with acute symptomatic Deep Vein Thrombosis [DVT] or Pulmonary Embolism [PE]). While the NOACs have certainly made significant advances in these indications, what else can we learn? Well, for starters, rivaroxaban, a direct Factor Xa inhibitor NOAC, is currently being studied in ambulatory cancer patients receiving chemotherapy who are considered at intermediate to high-risk (Khorana Score>2) for VTE. This trial, named 'CASSINI' is a Phase 3b randomized, double-blind, placebo-controlled, parallel-group multicenter study designed to assess the efficacy and safety of rivaroxaban compared to placebo for primary prophylaxis of VTE in ambulatory cancer patients.

Does any data already exist evaluating the use of NOACs in this space? Yes, findings from pooled subgroup analyses from previously conducted clinical trials support the hypothesis that rivaroxaban may be appropriate for effective VTE prophylaxis in cancer patients. For example, in the EINSTEIN-DVT and EINSTEIN-PE studies that evaluated rivaroxaban for both the treatment and secondary prevention of VTE, patients with cancer represented 8% of the total population studied. Of those patients with cancer, recurrent VTE occurred in 5% and 7% of patients receiving rivaroxaban and enoxaparin plus vitamin-K antagonist therapy, respectively. Also, clinically relevant bleeding occurred in 14% of patients receiving rivaroxaban and 16% of patients receiving enoxaparin [2].

It bears mentioning that there are a few distinguishing features between the design of the CASSINI study and other primary VTE prophylaxis studies conducted with other anticoagulants. First, the duration of previous studies was generally between 3 and 4 months. However, the risk of VTE has been shown to persist for longer, so the observation window in CASSINI was extended to six months. Another important feature of CASSINI, is the study's use of screening to detect asymptomatic VTE and exclude those patients from the trial [2].

This exclusion allowed for a common baseline for all the patients entering the trial. Once completed, the CASSINI study will be the first to offer data surrounding the long- term use of a NOAC for primary prevention of cancer-associated thrombosis [2]. Effective thromboprophylaxis in eligible, high-risk ambulatory cancer patients could lead to improved health outcomes and reduced associated health care costs. To note, the past cost-effectiveness of rivaroxaban in VTE prophylaxis and treatment in non-cancer patients was observed by Bamber et al. [7]. Their analysis reported that the use of rivaroxaban for the acute treatment and secondary prevention of VTE represented a "cost-effective choice" when compared with the standard of care, regardless of the required treatment duration [7]. This conclusion is also supported by analyses by Lefebvre et al. [8]. Remember, "*Medicine is not only a science; it is also an art. It does not consist of compounding pills and plasters; it deals with the very processes of life, which must be understood before they may be guided*" (Paracelsus).

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