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The challenge of hospital-related thrombosis

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In this issue of Blood, Heit et al provide epidemiologic data that the near-universal provision of prophylaxis for venous thromboembolism (VTE) to patients in acute care hospitals has not significantly reduced its overall incidence.1

In the United States, it is estimated that 600,000 cases of deep venous thrombosis and/or nonfatal pulmonary embolism occur each year.2 Hospitalization and nursing-home residence account for ~60% of these events.3 Several organizations, including governmental agencies and those charged with hospital accreditation, have called attention to this problem and implemented programs to increase VTE prophylaxis among hospitalized patients. The provision of anticoagulant prophylaxis to hospitalized patients at increased risk of thrombosis has therefore become widespread with the expectation that such practices would reduce the overall disease burden.

This paper examined the rates of incident and recurrent VTE, related and unrelated to hospitalization, among residents of Olmsted County, Minnesota during the period from 2005 through 2010; these rates were then extrapolated to the US population at large. The investigation of VTE in the Olmsted County population has been ongoing for many years and has provided valuable information with regard to its incidence and risk factors in the community.2,3 Over these 6 years, the proportion of patients receiving appropriate VTE prophylaxis increased from ~40% in 2006 to 90% in 2010. Despite this change, the rates of VTE related to hospitalization did not change significantly; 75% of cases were diagnosed within 3 months following discharge. For the 2008 to 2010 period, data regarding VTE prophylaxis were available from electronic medical records; the median durations of anticoagulant prophylaxis and hospitalization were 70 hours and 3 days, respectively. Because very few patients were given prescriptions for continued thromboprophylaxis at discharge, the authors hypothesize that the short duration of anticoagulation was a major factor contributing to the lack of a decline in the incidence of VTE.

Although the clinical benefit of anticoagulant prophylaxis in high-risk surgical patients was established >40 years ago, there have been uncertainty and controversy regarding its effectiveness in medical patients. The inclusion of asymptomatic deep venous thrombosis in the calf veins in the MEDENOX trial as a surrogate outcome may have led to an overestimation of the efficacy of anticoagulant efficacy (ie, enoxaparin) in preventing clinically important outcomes; the duration of anticoagulant therapy was also longer in this and other placebo-controlled trials of parenteral anticoagulants in the medically ill due in part to longer hospital stays. This makes the risk for bleeding associated with prophylactic anticoagulation seem minor in comparison with its efficacy in preventing venous thrombosis. In a review of VTE prophylaxis in hospitalized medical and stroke patients, Lederle et al concluded that heparin prophylaxis had no significant effect on mortality, may have reduced pulmonary embolism, and led to more bleeding and major bleeding events, resulting in little or no net benefit.5 Nonetheless, for acutely ill hospitalized medical patients at increased risk of thrombosis, the American College of Chest Physicians Evidence-Based Clinical Practice Guideline (9th edition) recommends thromboprophylaxis with low-molecular-weight heparin, low-dose unfractionated heparin (twice or 3 times daily), or fondaparinux (grade 1B), and suggests extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay (grade 2B).6

The implication of this study is that the implementation of “universal” in-hospital VTE prophylaxis programs has failed to impact real-world event rates. The results should not however be interpreted as showing that VTE prophylaxis among hospitalized patients is ineffective because nearly all “at-risk” patients received treatment, even if was of relatively short duration. Although abbreviated thromboprophylaxis due to decreased length of hospitalizations may have contributed to the results, other explanations are possible, including lack of efficacy of widely used anticoagulant regimens in high-risk populations, such as those with cancer.7 The study of Heit et al included surgical patients in addition to acutely ill medical patients. Many major surgical procedures are now done entirely in the outpatient setting or with overnight hospitalizations; this patient population also is likely receiving very short periods of thromboprophylaxis. This experience in Olmsted County highlights the need for ongoing research to identify patients at high risk for hospitalization or surgery-related
VTE such that they can be treated with an appropriate duration of antithrombotic therapy; such efforts are ongoing in the hospitalized medically ill with the direct oral anticoagulants.8,9

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REFERENCES


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A molecular roadmap for midostaurin in mastocytosis

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In this issue of Blood, Jawhar and colleagues describe the results of quantitative KIT D816V allele burden testing and next-generation sequencing of a panel of myeloid genes to characterize molecular correlates of response and progression on midostaurin therapy in patients with advanced systemic mastocytosis.1

On 28 April 2017, the US Food and Drug Administration approved the oral multikinase inhibitor midostaurin for the treatment of patients with newly diagnosed FLT3 mutation–positive acute myeloid leukemia in combination with chemotherapy and for patients with advanced subtypes of systemic mastocytosis (SM), such as aggressive systemic mastocytosis (ASM), SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL). Midostaurin’s target profile includes wild-type and D816V-mutated KIT.2 The oncocentric variant of KIT can be detected in 90% of SM patients with highly sensitive polymerase chain reaction assays.3 The identification of KIT D816V not only fulfills 1 minor diagnostic criterion for SM, but also informs the appropriate use of tyrosine kinase inhibitors for mast cell cytoreduction because this mutation is imatinib-resistant.

Patients with ASM, SM-AHN, and MCL share the common thread of reduced life expectancy, often related to progressive organ damage, complications of the associated hematologic neoplasm (AHN), or both. Neoplastic mast cells usually transit the blood as invisible marauders, plundering organs in their wake. The rarity of advanced SM and its protean manifestations of mast cell activation and organopathy often result in delayed diagnosis and treatment.

I think of advanced SM and late-stage myelofibrosis (MF) as “fraternal twins” because of their shared clinical and biological features. Patients often exhibit a hypercatabolic state with debilitating constitutional symptoms, hepato/splenomegaly, progressive organ impairment, and bone marrow failure with potential for transformation to acute myeloid leukemia (AML). The canonical driver mutations in SM and myelofibrosis, KIT D816V and JAK2 V617F, respectively, often coexist in a Darwinian ecosystem of multiple mutated clones. This is especially true in SM-AHN, whose genetic complexity partly reflects the marriage of 2 neoplasms, and stands in contrast to the comparatively bland clonal landscape of indolent SM that is usually restricted to KIT D816V.4 In both neoplasms, a similar set of genes influence prognosis: mutations in SRSF2, ASXL1, or RUNX1 (S/A/Rpos) adversely impact survival in SM;5 in primary myelofibrosis, mutations in SRSF2, ASXL1, EZH2, or IDH1/2 are associated with worse overall and/or leukemia-free survival independent of the Dynamic International Prognostic Scoring System–Plus scoring system.6 Several groups have used these molecular data to generate mutation-enhanced clinical prognostic models to optimize risk stratification for patients with advanced SM7 and myelofibrosis.

If advanced SM and myelofibrosis are fraternal twins, then midostaurin and ruxolitinib may be linked as a band of brothers, waging Sisyphean battles to reclaim disease control amid a minefield of mutations (see figure). Ruxolitinib produces marked improvements in splenomegaly and MF–related disease symptoms, but meaningful reductions in bone marrow fibrosis or JAK2 V617F allele burden are uncommon.8 In the pivotal global trial of midostaurin, the overall response rate was 60%, of which 75% were major responses, indicating normalization of ≥1 SM-related organ damage finding.9 In addition, a majority of evaluable patients experienced reduction in splenomegaly and/or a ≥ 50% decrease in the serum tryptase level or bone marrow mast cell burden. Decreases in spleen size with ruxolitinib and reversion of MF include midostaurin are clinically relevant beachheads in the fight against MF and SM that are inextricably associated with improved quality of life.
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