

# Out, Out Damn Clot: Anticoagulants Thin Out Cancer, Minimize Heredity

By Margaret Ragni, MD

**T**oday's exciting Education Session on Thrombophilia (9:30 – 11:00 a.m. and 4:00 – 5:30 p.m.) will focus on the role of thrombosis in cancer, the anticancer effects of anticoagulants, and the increasing use of anticoagulation as part of cancer treatment.

Agnes Yee, MD, MSc, McMaster University, will outline the biologic links between thrombosis and cancer. As many as 10 percent of patients with idiopathic thrombosis will develop cancer several years later, for a standardized incidence ratio of 2.1 to 4.6, with highest risk in the six to 12 months after thrombosis. As compared with cancer patients without DVT, those with DVT have shorter survival — 36 percent vs. 12 percent at one year after DVT. Although not evidence-based, strategies have been proposed to diagnose occult cancers following idiopathic DVT, guided by history, physical exam, and routine laboratory testing. A prospective study of 864 patients with idiopathic DVT by Monreal et al. determined that 56 percent of those with occult malignancy were identified by routine examination, although 23 percent of occult cancers remain undetected despite tests including tumor markers. Whether earlier diagnosis results in prolonged survival remains unanswered. However, evidence is mounting from several studies that treatment with low-molecular-weight heparins (LMWHs) provides a survival advantage for cancer patients. The thrombogenic potential of cancers has been attributed to tumor cell interaction with platelets, clotting and fibrinolytic proteins, endothelial cells, and host immune response. Tissue factor, found on all tumor cell surfaces, is induced and upregulated by TNF $\alpha$  and IL-8 released by tumor cells, and contributes both to thrombogenesis and angiogenesis, the latter through upregulation of VEG-F. Thus, LMWHs that interfere with TF/VIIa activation have anticancer potential. Clinical trials testing this hypothesis are in progress.

Paula Bockenstedt, MD, University of Michigan, will give the second talk on thrombosis risk assessment and appropriate management of inherited hypercoagulable states. As many as 50 percent of those with idiopathic DVT have congenital thrombophilia. Among these, the odds for first thrombosis can be generally differentially rated as *low* (OR 1.4) in heterozygous FV Leiden or prothrombin 20210A; *intermediate* (OR 2-11) in protein C, S, and antithrombin III deficiency; and *high* among those with more than one hereditary risk. DVT recurrence is six-fold higher with elevated factor VIII, and three-fold higher with hyperhomocysteinemia or antiphospholipid syndrome. Reducing recurrence requires prophylactic anticoagulation, but how long and how intense the anticoagulation should be is still not established. The ELATE trial shows that reduced intensity warfarin may maintain protection but at no reduction in bleeding risk compared with standard anticoagulation, and only delayed the time of DVT recurrence. Such studies beg the question of indefinite anticoagulation, but currently the American College of Chest Physicians guidelines only recommend the latter for individuals with homozygous or two or more heterozygous defects.

Ken Bauer, MD, Harvard Medical School, will complete the session with a review of newer anticoagulants. In attempts to overcome the shortcomings of standard warfarin and heparin, new anticoagulants in trials and in the clinic target single coagulation factors and achieve similar or better anticoagulant efficacy while reducing bleeding risk. These include direct thrombin inhibitors lepirudin and argatroban; the selective factor Xa inhibitor fondaparinux; and oral direct FXa inhibitors currently in clinical trials. FXa is an ideal target for new anticoagulant design, as it avoids the small amounts of thrombin that may escape inhibition by direct thrombin inhibitors while reducing bleeding risks. Fondaparinux induces a conformational change in antithrombin that increases its affinity for Xa, thereby potentiating the anticoagulant affect of fondaparinux. The efficacy of fondaparinux in DVT prevention following orthopedic surgery was shown in the EPHEBUS, PENTATHLON 2000, PENTAMAKS, and PENTHIFRA studies to be superior to the LMWH enoxaparin with similar bleeding risk.