

HEMOSTASIS AND THROMBOSIS IN CANCER**FACTORS CONTRIBUTING TO THE HYPERCOAGULABLE STATE IN CANCER PATIENTS**

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Cancer patients are at high risk of thromboembolic complications. Mechanisms related to the capacity of tumor cells to interact with and activate the hemostatic system of the host can play an important role in the pathogenesis of the thrombotic diathesis in these subjects. Additional prothrombotic effects are exerted by antitumor treatments (i.e., radio-, chemo-, and hormone therapies, as well as antiangiogenic therapies) and by general factors, such as bed-rest, previous history of thrombosis, inflammation, venous stasis. Cancer patients commonly present with multiple coagulation abnormalities. Elevated levels of plasma coagulation factors (i.e., fibrinogen and Factors V, VIII, IX, and X), increased levels of fibrin(ogen) degradation products (FDPs), and thrombocytosis have been the most frequent routine coagulation abnormalities reported in early prospective studies. More recently, abnormalities of plasma levels of sensitive thrombotic markers, underlying a hypercoagulable condition, have also been shown in the majority of cancer patients. Of particular interest are the measurements of the final products of blood clotting cascade reactions, including (1) peptides released during the proteolytic activation of coagulation system (i.e., prothrombin fragment 1+2, protein C activation peptide, Factors IX and X activation peptides, and fibrinopeptide A); (2) enzyme-inhibitor complexes (ie, thrombin *antithrombin complexes* [TAT] and *plasmin* antiplasmin complexes); and (3) D-dimer, a cross-linked fibrin degradation product.

Several studies have determined plasma levels of these markers in cancer patients at different stages of disease but, to date, the clinical utility of these markers in predicting thrombosis in an individual patient has not been clarified. There have been no large prospective studies to correlate the levels of circulating markers with objectively confirmed thrombotic events. Therefore the value of determining circulating levels of these laboratory markers prior to surgery or chemotherapy in assessing the risk of thrombosis in an individual cancer patient remains unclear. Large, prospective, randomized clinical trials are necessary to clarify the clinical role of these markers in the management of thrombotic complications associated with malignancy.

Interestingly, in the setting of cancer survival, studies are increasingly demonstrating that high levels of these markers correlate with severity of disease and poor prognosis. Specifically, the data suggest that the degree of hypercoagulability may predict the risk of death from cancer.

EMERGING LINKS BETWEEN THROMBOSIS, INFLAMMATION AND CANCER: ROLE OF HEPARINS

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Heparin and its improved version LMWH are known to have poly-pharmacological actions at various levels. Earlier studies focused on the plasma anti-Xa and anti-IIa pharmacodynamics (PD) for the different LMWH. Other important PD parameters for heparin and LMWH might explain the diverse clinical impacts of this class of agents in thrombosis and beyond. These diverse pharmacological actions include the release of the vascular tissue factor pathway inhibitor (TFPI), inhibition of key matrix degrading enzymes, inhibition of selectins (P, E, and L-selectins), and other mechanisms. LMWHs have different capacity to affect the above mechanisms based on differences in the method of manufacturing, molecular weight distribution, and degree of sulfation. There are several evidences for the key role of LMWH in hypercoagulation in thrombosis & cancer, angiogenesis, and inflammatory disorders. In that regard, many cancer patients reportedly have hypercoagulable state, with recurrent thrombosis due to the impact of cancer cells and chemotherapy or radiotherapy on the coagulation cascade. Studies have demonstrated that UFH or its low molecular weight fractions interfere with various processes involved in tumor growth and metastasis. These include fibrin formation, binding of heparin to angiogenesis growth factors such as basic fibroblast growth factor (b-FGF), modulation of tissue factor, and perhaps other more important modulatory mechanisms such as enhanced TFPI release and inhibition of various matrix-degrading enzymes. Clinical trials have suggested a clinically relevant and improved efficacy of LMWH, as compared to unfractionated heparin (UFH) on the survival of cancer patients (tumor type and stage) with deep vein thrombosis. Studies from our laboratory demonstrated a significant role for LMWH, non-anticoagulant heparin derivatives, and LMWH releasable TFPI and the anti-selectins on the regulation of angiogenesis, tumor growth, and tumor metastasis. Thus, modulation of tissue factor / VIIa non-coagulant activities by LMWH releasable TFPI plus the anti-selectins activity by heparin moieties provided expanded clinical utilities for heparin and derivatives in inflammation and angiogenesis associated disorders including human tumor growth, metastasis, and inflammatory disorders.