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Editorial

Heparin treatment of malignancy: the case for clinical trials in colon cancer

In this issue of Thrombosis Research, Pross et al. report inhibition by a low-molecular-weight heparin (LMWH), Reviparin, of adhesion and invasion of adenocarcinoma cells in vitro and of tumor growth in rats following intraperitoneal injection of colonic adenocarcinoma cells. Reviparin inhibited growth of tumors implanted intraperitoneally in a dose-dependent manner. Greater inhibition of tumor growth was achieved with subcutaneous compared to intraperitoneal drug administration. They postulated that this approach might be worthy of investigation in patients having minimally invasive laparoscopic procedures for intra-abdominal malignancy.

This study is a welcomed addition to a series of reports of effects of heparins in animal models of malignancy (reviewed in Refs. [1–3]). These have shown that heparins, and especially the LMWHs, intercept several tumor growth regulatory pathways. For example, heparin inhibits tumor and angiogenic growth factors, heparinases that enhance tumor cell invasiveness and alter the orderly interaction of growth factors with the cell surface, tumor cell-induced thrombin generation, and platelet clumping on embolic tumor cells necessary for metastatic dissemination (among other effects). Heparin releases tissue factor pathway inhibitor (TFPI), an anti-angiogenic peptide, from the vascular endothelium. LMWH appears to be superior to unfractionated heparin for many but not all of these activities.

Data of Pross et al. showing heparin effects on colonic adenocarcinoma growth in vivo are a reminder that while malignancy in general may be conceived of as a solid-phase coagulopathy, the manner of interaction of tumors with relevant pathways differs according to tumor type [1,2]. Thus, translation of findings from model systems to clinical trials is best accomplished by considering the sum total of data on the coagulation biology of individual human tumor types. We last reviewed the coagulation biology of colon cancer in 2000 [4]. Literature available then indicated that heparin blocked the activity of several growth factors required for colon cancer growth. Higher levels of these growth factors in body fluids and tumor tissues predicted poorer patient outcome. Several clinical trials of heparin prevention of deep vein thrombosis (DVT) with surgical resection of colonic malignancy showed improved patient outcome in patients receiving heparin. A meta-analysis of clinical trials comparing unfractionated versus LMWH for DVT treatment showed a strong trend toward improved survival in the subset of patients having DVT in the setting of colon cancer.

Since that earlier review, the literature on heparin effects on malignancy in general and on colon cancer in particular has expanded. For example, heparin binding to platelet P-selectin blocked metastasis of circulating human colonic cancer cells injected into immune-deficient mice [5]. Vascularization and growth of human colon cancer mass lesions in the chick chorioallantoic membrane model were halted by LMWH treatment [6]. Favorable clinical effects of heparin have been described in the past in numerous case reports, cohort studies, and randomized clinical trials [1,2]. Recent literature includes a report of a case of metastatic colon cancer that remitted following heparin treatment for an intercurrent episode of DVT [7] and a case in which heparin was considered to have interrupted hepatic metastasis from colon cancer [8]. Perusal of the online abstracts form the 2003 ASCO meetings disclosed three clinical trials of LMWH intended to alter the natural history of malignancy [9]. In abstract 846, Lee et al. reported a further analysis of a comparative trial of long-term dalteparin versus warfarin for treatment of cancer-associated DVT. While no difference was observed in cancer outcome for all patients combined, a significant improvement in 12-month survival was described ($p = 0.03$) for the subset of patients without metastatic disease at entry to the study. In abstract 1149, Icli et al. described the results of a randomized trial of combination chemotherapy with versus without nandroparine in patients with advanced pancreatic cancer. Addition of LMWH (compared to chemotherapy alone) improved tumor response rates (64.7% versus 12%, $p = 0.001$), median time to progression (6 months versus 3 months, $p = 0.0001$), overall median survival (9 months versus 4 months, $p = 0.0034$), and 1 year survival (47.7% versus 13.5%, $p = 0.029$). In abstract 1751, Moyano et al. reported the results of a phase II trial of chemotherapy plus enoxaparine in a cohort of patients with advanced, hormone refractory

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prostate cancer. The authors concluded that this combination had ''activity'' in this tumor type based on reduction of PSA levels.

While definitive clinical trials of LMWH in colon cancer have not been reported, this approach is feasible using currently available LMWHs. Pharmacologic properties of the LMWHs render this class of drugs suitable for clinical trials requiring long-term self-administration on an outpatient basis [3]. LMWHs can be given readily along with other cancer treatments. Ample justification exists on mechanistic grounds for randomized clinical trials that must be controlled for disease stage, performance status, and standard anticancer treatment. Ancillary laboratory and scanning procedures should provide information on mechanisms of heparin effect on cancer growth. Favorable results would constitute a ''test-of-concept'' to guide subsequent drug development [10,11]. For example, heparin species designed to intercept pathways relevant to a given tumor type but lacking undesirable characteristics (e.g., bleeding risk) might be tested. In addition, evidence has implicated the urokinase-type plasminogen activator (uPA)–plasmin system in the pathogenesis of colon cancer [12,13]. Marked improvement in the course of colon cancer has been reported using aprotinin that inhibits this system [12,13]. Signaling cross-talk between heparin-binding growth factors and expression of tumor cell urokinase suggests that partial benefits realized with either drug alone might be amplified by testing them in combination.

The fact that the heparins do not resemble traditional anti-neoplastic agents may account for the fact that their ability to retard tumor growth has largely been overlooked. However, the prospect that this familiar class of drugs may have efficacy while lacking the toxicities typical of standard anticancer therapies challenges the imagination. Hopefully, the clinical trials envisioned by Pross et al. will soon become a reality.

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