Vitamin K, warfarin and prothrombin: an alternate pathway to improve cancer survival

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Billroth first proposed a theoretical relationship between hemostatic mechanisms and the development of cancer metastasis in 1878. A lack of experimental animal models to study cancer metastasis inhibited further studies on hemostasis and cancer until the late 1960s and early 1970s.[1] Since that time, studies using mouse and rat models, have demonstrated a reduction of tumor metastasis and improved animal survival with systemic anticoagulation. However, the therapeutic benefits observed in these models cannot be attributed to a single, specific intervention in the coagulation system since a variety of anticoagulants, anti-platelet and fibrinolytic agents appeared to be effective.[1] Warfarin was utilized in many of these experiments since it had demonstrated efficacy and reasonable safety in long-term use in man. Although warfarin was effective in reducing metastasis in a majority of these animal models, the degree of anticoagulation and methods of monitoring varied significantly. Although a number of alternate mechanisms for warfarin effectiveness have been postulated independent of its anticoagulant effect, such as a direct inhibition of tumor replication or enhancement of the anti-tumor immunity, experimental studies in which oral warfarin was combined with simultaneous oral vitamin K firmly established that warfarin's anticoagulant effect was necessary for its anti-metastatic effect.[2] Clinical studies on the effect of warfarin in human malignancy are limited and less than conclusive. A number of small, uncontrolled clinical studies suggested a benefit in a variety of malignancies. The US Veterans Administration Cooperative Study 75 reported a statistically significant doubling of survival for patients with small cell lung cancer who were treated with chemotherapy and warfarin in a randomized trial.[3] However, subsequent treatment studies with warfarin in patients with small cell lung cancer by the Cancer and Leukemia Group B were less definitive. In addition, a lack of clinical benefit with warfarin anticoagulation has been reported in colon, prostate, non-small cell lung cancer and advanced breast cancer.

A surprising report by the Duration of Anticoagulant Trial investigators found significantly fewer genitourinary malignancies in the patients treated with vitamin K antagonists for six months compared to subjects treated for six weeks with a mean follow up of 8.1 years.[4] The decreased incidence of de novo malignancies observed in this trial would suggest a possible direct effect of warfarin on the process of malignant transformation. However, a similar randomized trial of vitamin K antagonist treatment of VTE for 1 year compared to 3 months failed to find a reduction in the incidence of overt cancer at a mean follow-up of 43 months.[5]

There are a number of theoretical mechanisms by which warfarin could impact cancer survival. If the primary mechanism, suggested by animal models, is due to its anticoagulant effects, there are several steps in the coagulation cascade were warfarin might act. These could include reduced Factor VIIa-tissue factor formation and signaling, reduced Factor Xa and thrombin generation with reduced tumor PAR activation, and decreased thrombin-mediated platelet activation which would result in decreased release of platelet growth factors or by reduced fibrin formation as a substrate for metastatic growth. In 1984, we reported the synthesis of des-γ-carboxyprothrombin (DCP) by hepatocellular carcinomas (HCC) due to an acquired defect in γ-carboxylation by the tumor and that this could serve as a tumor marker for this malignancy.[6] Subsequent studies confirmed that under-carboxylated prothrombin species were produced by two thirds of hepatomas.[7] Recent Japanese studies have reported that patients with increased blood levels of DCP, with low or undetectable blood α fetoprotein, had slower growing and more limited tumors. In collaboration with Dr Brian Carr, we have evaluated the effect of DCP on HCC growth *in vitro*. Pro-

thrombin was found to be a potent growth stimulus for HCC in culture. Its growth effects could be inhibited by the addition of hirudin, suggesting that prothrombin's growth stimulatory effect occurred as a result of its conversion to thrombin. DCP, with an intact thrombin domain as shown by E. carinatus activation, had no stimulatory effect on HCC growth in culture. These studies suggest that the ability of warfarin to affect survival in select malignancies could result from reduced local thrombin generation and therefore, reduced PAR stimulation. This observation has encouraged us to design a clinical trial of warfarin anticoagulation after chemoembolization of DCP positive hepatomas.

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