Review Article

Anticoagulation, ferrotoxicity and the future of translational lung cancer research

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Abstract: Numerous studies have shown that elements of coagulation reactions mediate tumor cell proliferation, motility (invasiveness), tissue remodeling and metastasis. Coagulation activation is virtually a universal feature of human malignancy that differs from the clotting response to injury in that it is self-perpetuating rather than self-attenuating. Coagulation activation participates in tumor matrix deposition and local inflammation, and predicts subsequent cancer risk and adverse cancer outcomes. Several clinical trials of anticoagulants have shown improved outcomes in small cell carcinoma of the lung (SCCL) that have been correlated with assembly on the tumor cells of an intact coagulation pathway. However, variable efficacy of anticoagulant therapy has raised doubts about the coagulation hypothesis. Recently, initiators of coagulation and fibrinolytic pathways have been identified that mediate tumor inception and progression. Notable among these is oxidative stress driven by iron-catalyzed reactive oxygen species that may be the basis for local coagulation activation, tumor matrix deposition, inflammation and aberrant properties characteristic of the malignant phenotype. Recognition of important biological characteristics of individual tumor types, disease stage, choice of standard therapy including chemotherapy and the iron status of the host may clarify mechanisms. All of these are subject to modification based on controlled clinical trial design. Further tests of the coagulation hypothesis may lead to novel, low cost and relatively non-toxic approaches to treatment of malignancy including lung cancer that contrast with certain current cancer treatment paradigms.

Keywords: Blood coagulation; cancer treatment; iron

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The advent of anticoagulant treatment for cancer

Beginning in the 1950's and extending for over a half century thereafter, scores of studies in experimental malignancies documented inhibition of tumor growth and metastasis by manipulation of the coagulation mechanism. The extensive literature on this subject has been reviewed in detail in the past (1,2) and will be highlighted here briefly as background for subsequent translational steps to treatment of human malignancy.

Heterogeneity in responsiveness between experimental tumor types to a variety of coagulation-regulatory interventions was recognized from the outset. However, extensive use of treatment controls had confirmed that benefits were indeed due to drug interference with the coagulation mechanisms (1,2). Reference to these early studies has focused on the concept that intervention was "anti-metastatic". Certain studies had shown reduction in metastatic takes (typically lung colonies following tumor cell infusion) with treatment. A more faithful interpretation of the pre-clinical evidence shows that the clotting mechanism in broad context regulates cell proliferation, motility and invasion, and tissue remodeling as well as metastasis (1-5). Coagulation laboratory test abnormalities and venous thromboembolism (VTE) that signal adverse cancer outcomes invited translation of experimental results to clinical trials. The blood coagulation mechanism

is fundamentally deranged in cancer and, unlike the physiologic response to injury, apparently incapable of self-attenuation (3). Clinical trials were considered feasible because anticoagulation of the blood had long been used to prevent and treatment VTE in malignancy. Such treatment had not yet been studied for effects on cancer outcomes.

Heterogeneity of responses between experimental tumor types signaled the importance of defining mechanisms of the coagulation-cancer interaction in human disease as clinical trials with warfarin commenced. Consistency of responses in given experimental tumors having malignant cells with properties that varied according to tumor type, such as dominant pro-coagulant versus pro-fibrinolytic enzymatic pathways, led to cautious clinical trial design. Mechanisms in human tumor types had to be elucidated individually. Laboratory reagents suited to studies in human tumor tissues disclosed assembly of blood coagulation pathways *in situ* in various patterns on tumor, vascular endothelial or inflammatory cells (1,2). Probes for the active serine site of thrombin (6) and activated factor X (Xa) (7), and for intact fibrinogen versus exposed thrombin cleavage sites on fibrinogen (8) signified cell-specific coagulation activation micro-anatomically within the tumor bed in intact tumor tissues. Analyses were conducted on tumor types studied in the original clinical trial of warfarin described below (9,10) including colon, head and neck, prostate, non-small cell lung NSCLC) and small cell carcinoma of the lung (SCCL). Of these, only SCCL showed an intact coagulation mechanism with generation of enzymatically active factor Xa and thrombin, and chemically defined fibrin associated with tumor cells *in situ* (6-8). Among these tumor types, only SCCL appeared to respond favorably to warfarin anticoagulation (9,10). Combined clinical and laboratory findings in SCCL led to the hypothesis that warfarin may alter human tumor growth by attenuating tumor cell-initiated coagulation activation in SCCL. Benefits of warfarin were not likely due to systemic anticoagulation because such activation is common to many tumor types and anticoagulants treated successfully DVT with various malignancies but failed to alter outcomes in certain other tumor types (3). An "anti-metastatic" mechanism was considered unlikely because all tumor types metastasize, all were apparently comparably anti-coagulated, and survival curves by randomization overlapped for all tumor categories—the exception being SCCL. Conclusion: the occurrence of local coagulation activation may enhance growth and dissemination of established disease in SCCL. Subsequently, two additional tumor type-specific prospective randomized clinical trials were conducted with warfarin (for a total of three trials of warfarin) and four with heparins in SCCL. Although patterns of outcomes varied between clinical trials, evidence suggested that SCCL responded to anticoagulation.

Results from these trials in SCCL are reviewed chronologically in the context of a recently completed trial of the low molecular weight heparin (LMWH), dalteparin, in which no effect on survival was found in either SCCL or NSCLC. Anticoagulant effects on tumor response and survival, salient design characteristics, confounders potentially capable of impacting outcomes differentially and incentives for future translational research are discussed.

1981

Zacharski *et al.* VA Cooperative Study #75 (9,10). Previously untreated patients were randomized independently into six separate clinical trials conducted concurrently in five different tumor types. Each trial was designed separately according to patient sample size requirement, organ of origin by histology, disease stage, standard therapy and follow-up procedures. Analysis was not of "sub-groups" of a heterogeneous population of cancer patients entered to a single study. At the time this study began (in the mid 1970s) the utility of sorting NSCLC by disease stage and of distinguishing SCCL from NSCLC were recognized but sorting according to limited versus extensive SCCL was not. Each tumor category was assigned appropriate standard treatment and followed separately for outcomes. Survival was the primary endpoint.

A preliminary report (9) described fifty patients with SCCL that received combination chemotherapy plus radiation therapy and were randomized to warfarin versus no anticoagulation. Warfarin was discontinued with disease progression. Significantly improved time to disease progression was observed with warfarin treatment (P=0.030) and in survival in patients failing to achieve a complete or partial response (P=0.033). Median overall survival was doubled with warfarin, 50 versus 24 weeks in controls (P=0.02), and in patients with extensive disease at entry (P=0.049). The clinical trial of warfarin in SCCL was terminated by the Data Monitoring Board because results were statistically significant and adriamycin became approved for SCCL treatment the addition of which would require protocol modification. The results were considered interesting and confirmation would be required.

1984

Zacharski *et al.* VA Cooperative Study #75 (10). This final report described 431 patients with limited or disseminated NSCLC; advanced colon, head and neck, and prostate cancer; and SCCL. Too few patients with limited extent NSCLC were entered for evaluation. No effect of warfarin was observed for any tumor type (survival curves were overlapping) except SCCL. Improvement in SCCL of time to disease progression (P=0.016) and survival with versus without warfarin (49.5 versus 23 weeks, P=0.018) after longer follow-up was confirmed. Survival in patients with extensive disease at randomization also improved with warfarin (P=0.013).

1989

Chahinian *et al.* Cancer and Leukemia Group B (CALGB) protocol 8084 (11). A total of 294 evaluable patients with extensive SCCL stratified for sex and performance status were entered. Randomization was to one of two different advanced combination chemotherapy regimens abbreviated here as MACC and alternating MEPH/MACC. Patients receiving MACC were than randomized to warfarin (MACC + W) versus no warfarin anticoagulation. Complete and partial tumor response rates were significantly increased in the MACC + W regimen (17% and 50% respectively) when compared to MACC alone (8% *vs*. 43%) or MEPH/MACC, 10% versus 38% respectively (P=0.012). Complete response rates doubled with addition of warfarin to MACC chemotherapy. Two way comparisons showed improved response rates with warfarin compared to MACC alone (P=0.027) and compared to MEPH/MACC (P=0.005). No differences in response rates were observed on comparison of chemotherapy regimens without warfarin. Both failure-free (P=0.054) and overall (P=0.098) survival were increased with MACC+W compared to either combination chemotherapy regimen without warfarin. The complex design of these studies suggested that goals were to improve outcomes with chemotherapy rather than to clarify the role of the coagulation mechanism in SCCL progression.

1994

Lebeau *et al.* "Petites Cellules Group" protocol 02-PC85 (12). A total of 277 patients with SCCL received combination chemotherapy and were randomized to receive or not receive 500 IU/kg/day of unfractionated heparin (UFH) daily in two or three divided doses for 5 weeks. Compete response rates were 37% with UFH versus 23% without UFH, P=0.004. Median survival with UFH was 317 days versus 261 days without UFH, P=0.01. Survival was also improved at 1, 2 and 3 years of follow-up. Improved survival was observed with UFH in the subgroup of patients with limited extent of disease at randomization, P=0.03.

1997

Maurer *et al.* CALGB protocol 8532 (13). Favorable results in extensive SCCL in protocol 8084 prompted a randomized clinical trial in previously untreated limited extent SCCL. A total of 369 patients received an aggressive alternating combination chemotherapy regimen with randomization to warfarin versus no anticoagulation. Unacceptable toxicity from combination chemotherapy required modification of standard therapy during the study. Patients treated according to the original protocol plus warfarin experienced marginally improved failure-free survival with warfarin (P=0.07). A landmark analysis in complete responders at 8 months of follow-up showed improved median survival with warfarin compared to no warfarin (33 *vs*. 13.75 months, P=0.05).

2004

Altinbas *et al.* (14). Eighty-four previously untreated patients with SCCL were admitted to a clinical trial in which all patients received combination chemotherapy and radiation therapy and then randomized to receive 5,000 U of the LMWH, dalteparin, subcutaneously daily for 18 weeks or standard therapy only. Overall tumor response rates were 42.5% with standard treatment and 69.2% with addition of dalteparin (P=0.07). Median progression-free survival for the entire cohort was 6 months with standard therapy alone versus 10 months with addition of dalteparin (P=0.001). Overall median survival for the entire cohort was 8 months with standard treatment alone versus 13 months with addition of dalteparin (P=0.01). Risk of death in the dalteparin-treated group was 0.56, 95% confidence interval (CI) (0.00–0.86), compared to standard therapy alone (P=0.012). Overall survival was improved in the dalteparin-treated group in patients with both limited (P=0.007) and extensive disease (P=0.01) at entry.

2009

Green D, and Kwaan HC, editors: Coagulation and

Cancer, Springer, NY (15). This book summarized the extensive literature linking coagulation activation to the epidemiology, pathogenesis and course of malignancy. Optimism regarding the prospects of favorable outcomes with anticoagulant, and particularly LMWH, treatment of cancer was reflected in chapter 15 entitled "Effects of anticoagulants on cancer: heparin" by Pineo and Hull. Favorable effects of heparins and related compounds in experimental and human malignancies were reviewed together with the multiplicity of mechanisms by which this class of drugs might exert their effect. Data from a number of prior studies were reviewed, including one meta-analysis, suggesting superior effects of LMWH on cancer outcomes. Data from two large prospective randomized trials comparing UFH with LMWH for VTE treatment were subjected to *post hoc* multiple logistic regression analysis by Green *et al.* (16) for comparative effects of heparins on mortality in the subset of patients with malignancy having VTE entered to these studies. Combined cancer mortality was 31% (21 deaths among 67 patients) in UFH-treated patients and 11% (7 deaths among 76 patients) in LMWH-treated patients, P=0.005. While analysis was *post hoc*, the survival advantage with LMWH was not considered attributable to confounding by tumor stage or possible detrimental effects of UFH. Both groups were comparably anticoagulated suggesting that superior effects of LMWH on the course of malignancy might best be explained by non-anticoagulant mechanisms.

2013

Lecumberri *et al.* the ABEL study, ClinicalTrials.gov identifier: NCT00324558 (17). Thirty-eight patients with previously untreated limited disease SCCL were entered. All patients received standard combination chemotherapy and radiation therapy. Patients were randomized to receive standard therapy alone or the LMWH, bemiparin, 3,500 units once daily for the 26 week duration of standard therapy. Median progression-free survival in the control group was 272 versus 410 days with addition of bemiparin (hazard ratio, 2.58; 95% CI, 1.15–5.80; P=0.022). Median overall survival was 345 days with standard therapy alone and 1,133 days in the bemiparin group (hazard ratio, 2.96; 95% CI, 1.22–7.21; P=0.028). After 1 year of follow-up, 90% of bemiparin-treated versus 41% of control patients were alive (P=0.040). After 2 years of follow-up, 71% of bemiparin-treated versus 35% of control patients were alive (P=0.042). Tumor response rates were similar in both study arms.

2016

Macbeth *et al.*, the FRAGMATIC trial (18,19). A randomized phase III clinical trial was conducted in which 2,202 patients with newly diagnosed NSCLC or SCCL received standard therapy and were randomized to receive either no experimental treatment or the LMWH, dalteparin, 5,000 U once daily subcutaneously, for 24 weeks. Patient randomization was stratified according to cell type, SCCL or NSCLC, sex, performance status, extent of disease and medical center. Analysis of the total cohort showed an anticoagulant effect of treatment with a significant reduction in risk of DVT (P=0.001). No difference in overall or progression-free survival was found. Entry of 150 patients with limited extent SCCL and 242 patients with extensive SCCL permitted analysis of LMWH effects on survival. *Post hoc* analysis showed no difference in hazard ratios for mortality or in survival on Kaplan Meier analysis for SCCL patients randomized to dalteparin versus control.

Current status of anticoagulant effects on cancer outcomes

In 2011, Lebeau *et al.* (20) surveyed retrospectively outcomes in 239 patients with SCCL seen between 1990 and 2002 in an oncology practice setting at a single center. Of these, 55% received a form of heparin in addition to standard therapy. Outcomes were sorted for this report according to the combination chemotherapy used, age at diagnosis, sex, smoking status, extent of disease and heparin use. Overall, stage-specific survival was approximately doubled with heparin on univariate (P=0.01) and multivariate (P=0.018) analysis. In 2014, Altinbas *et al.* (21) reviewed retrospectively data on patients reported previously (14) including 67 patients with SCCL treated with combination chemotherapy plus dalteparin. Circumstantial evidence favoring prolonged dalteparin therapy was presented. Data from a phase II trial of combination chemotherapy plus an infusion of pro-fibrinolytic urokinase plasminogen activator in 27 patients with limited extent SCCL reported an 85% complete response rate. Urokinase infusion in 24 patients with extensive disease resulted in a 71% complete response rate (22). Median survival with urokinase treatment was 26.3 months with limited and 13.3 months with extensive disease SCCL. A randomized trial of standard therapy plus aspirin versus no aspirin showed no effect of this treatment on cancer outcomes in SCCL (23).

The concept that the coagulation mechanism may

support cancer progression remains unfamiliar to many. Coagulation activation in malignancy is easily dismissed as an annoying "paraneoplastic" phenomenon of no further consequence. Earlier studies of anticoagulant effects on survival in SCCL have been faulted as "underpowered" owing to the small number of patients entered. This criticism may require reconsideration. Coagulation reactive drugs may not seem like other anti-cancer agents—primarily because they are not like others. The clotting mechanism may mediate malignant progression by multiple mechanisms (1-4) and individual drugs may have a variety of mechanisms of effect (5,15). Blood coagulation is a precariously balanced system that may be tipped toward either too much or too little (coagulation) with seemingly minimal provocation. Persistent elevation of markers of systemic coagulation activation has been shown to be strong predictors of subsequent long-term cancer risk (24). Chemotherapeutic agents induce tumor cell procoagulant activity that may negate attempts to attenuate their reactivity (25). Such effects may account for the apparently reduced efficacy of warfarin in CALGB protocol 8532 (13) compared to 8084 (11). Markers of coagulation activation predict subsequent tumor responsiveness in SCCL (26-28). Regardless of disease stage, elevated levels of fibrinogen and D-dimer before treatment and after two cycles of chemotherapy were independent predictors of unfavorable progression-free and overall survival (28). Markers of systemic thrombin activation are normally counterbalanced by a proportionate increase in markers of compensatory fibrinolysis. The ratio of markers of thrombin to fibrinolysis is disproportionately elevated with SCCL (29). The degree of thrombin relative to fibrinolytic activity predicts subsequent poor tumor response in SCCL. Patients in long-term remission had a near normal ratio.

Tumor stage may also influence outcomes with anticoagulant therapy. In 2000, von Tempelhoff *et al.* (30) reported long-term pelvic and breast cancer outcomes from a prospective randomized double-blind trial of LMWH (140 evaluable patients) versus UFH (147 evaluable patients) for inter-operative VTE prevention. Evaluation at 650 days showed significant long-term improvement in survival with LMWH compared to UFH (P=0.006) particularly in pelvic cancers but also in breast cancer patients with adverse markers of risk. In 1983, Kohanna *et al.* (31) reported a retrospective analysis of a cohort of 230 patients with resected Dukes B and C colon cancer seen at a single institution from 1973 through 1977. Of these, 180 received of pre-operative prophylactic UFH for VTE prevention continuing daily until hospital discharge and 50 demographically comparable patients received no anticoagulation. On long-term follow-up overall mortality was 54% in the control group and 35% with UFH. Life table analysis revealed a consistently lower overall mortality in the UFH-treated group throughout the follow-up period, P<0.05, although cause-specific mortality was not different.

Variability in outcomes with anticoagulants in SCCL, and particularly the negative results by Macbeth *et al.* (19), invite consideration of potentially contributory factors to systemic coagulation activation besides use of chemotherapy (25). Most intriguing is evidence for interactions with elevated levels of body iron that parallel markers of coagulation as indicators of cancer risk (32-35). Iron-catalyzed hydroxyl ion activates coagulation (36) and results in tumor deposition of a modified fibrin that adversely effects cancer outcomes (37) and resists physiologic thrombolysis (38). Notable effects include the ability of iron to trigger tissue procoagulant activity (39) and tumor cell urokinase expression (40). Delivery of an iron load may explain why blood transfusion has a negative impact on malignant growth (41,42). Aberrant tumor cell iron handling is central to its toxicity (43,44). Studies underway should clarify effects of iron in experimental (45-47) and human (48-50) malignancy. Little information is available on effects of iron reduction on blood coagulation.

Conclusions

The potential importance of anticoagulant effects in cancer, while variable, should not be discounted. The challenge may be to consider explanations for findings that may not be obvious at first glance, but nonetheless signal unprecedented opportunities for progress in cancer prevention and treatment. New peptide anticoagulants with specificity for the active serine site of factor Xa and thrombin should gain access readily to the extravascular environment of cancer (51) needed for inhibition of tumor progression (52). Clinical trials may be indicated in tumor types, such as malignant melanoma (6,7,53-56) and renal cell carcinoma (6,7,57), having tumor cell induced coagulation activation similar to that of SCCL. Transition from the dominant "search-and destroy" paradigm to less toxic and expensive translational strategies offer the prospect of improved cancer prevention and treatment and even the possibility of increased self-management (58).

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Footnotes

Conflicts of Interest: The author has no conflicts of interest to declare.

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