Long-Term Coagulation Changes after Resection of Thoracoabdominal Malignancies

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BACKGROUND: The purpose of this study was to evaluate the long-term coagulation status of patients undergoing malignancy resection.

STUDY DESIGN: A prospective observational trial was conducted with informed consent in 52 patients (age 66 ± 10 years and 60% male) with thoracoabdominal tumors (pancreas [n = 18, 35%], esophagus [n = 13, 25%], liver [n = 7, 14%], stomach [n = 6, 12%], bile duct [n = 3, 6%], retroperitoneal [n = 3, 6%], and duodenum [n = 2, 4%]) with 6- to 12-month follow-up. Coagulation was evaluated with rotational thromboelastography (ROTEM) on whole blood and with a panel of hemostatic markers on stored plasma.

RESULTS: Maximum clot firmness (MCF) in the intrinsic, extrinsic, and fibrinogen pathways increased immediately postoperatively and then decreased by 9.2 ± 4.1 months ($p < 0.05$). Markers of thrombin generation (prothrombin fragment 1 + 2, fibrinolysis [D-dimer], and endothelial activation [coagulation factor VIII]) were elevated at all time points. The ROTEM pattern depended on histologic type and cancer location. All esophageal tumors were adenocarcinoma and demonstrated similar patterns to the overall population, with MCF differences over time in all 3 pathways (all $p < 0.05$). Regarding tumors of the pancreas or liver, there were no statistically significant differences when comparing all 3 time periods, but there were time-related differences when evaluating only primary adenocarcinomas of the liver (all $p < 0.05$). Three patients (6%) developed venous thromboembolism (VTE) and had decreased clot formation time, increased angle, and increased MCF (all $p < 0.05$).

CONCLUSIONS: Cancer patients at risk for VTE can be identified with a point-of-care ROTEM test and may benefit from additional anticoagulation. Biomarkers reflecting different functional hemostasis activity groups (fibrinolysis, thrombin generation, and endothelial activation) confirm the ongoing prothrombotic state. The ROTEM demonstrated increased hypercoagulability post-operatively, which returned to baseline in long-term follow-up. Reversal of cancer-induced hypercoagulability occurred in some patients and varied with tumor histology and location. (J Am Coll Surg 2014;218:846–855. © 2014 by the American College of Surgeons)

The association between hypercoagulability and cancer was first reported by Trousseau in 1865.[1] Hypercoagulability of cancer can be attributed to patient characteristics (age and medical comorbidities[2,3]), tumor-specific factors (expression of tissue factor[4]), and iatrogenic factors (chemotherapy and operative intervention[5]). Venous thromboembolism (VTE) rates are increased in cancer patients, and VTE is the most common cause of preventable 30-day surgical mortality.[3,6-8]

Theoretically, surgical resection of cancer should reverse hypercoagulability. However, we previously reported that hypercoagulability worsens immediately after cancer resection and persists for at least 1 month postoperatively.[9] Because there is limited information on this subject, the main purpose of this study was to follow-up our initial findings and prospectively evaluate the long-term coagulation status of patients undergoing operative resection of malignancies. We hypothesized that

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Abbreviations and Acronyms

CFT = clot formation time
CT = clot time
DVT = deep vein thrombosis
EXTEM = extrinsic coagulation pathway
FIBTEM = EXTEM based assay for fibrin part of clot
INTEM = intrinsic coagulation pathway
MCF = maximum clot firmness
PE = pulmonary embolism
PT = prothrombin time
ROTEM = rotational thromboelastography
TEG = thromboelastography
VTE = venous thromboembolism

cancer-induced hypercoagulability is reversed after resection during a 6- to 12-month follow-up.

Rotational thromboelastography (ROTEM) is a point-of-care viscoelastic hemostatic assay that provides a comprehensive overview of coagulation. It has been used to diagnose coagulopathy and predict massive transfusion in trauma patients[10-12] and to evaluate hypercoagulability in cancer patients.[13,14] In this study, ROTEM on fresh whole blood was compared with a panel of hemostasis markers on stored plasma.

METHODS

An IRB-approved prospective observational study was performed with informed consent at the University of Miami/Jackson Memorial Hospital and Sylvester Comprehensive Cancer Center. Patients undergoing potentially curative resection of malignancy were enrolled starting in February 2011 and followed postoperatively until May 2013. Inclusion criteria were malignant tumors of the upper gastrointestinal tract (esophagus, stomach, duodenum), pancreatobiliary system (pancreas, bile duct), liver, and retroperitoneal tumors. Exclusion criteria were benign or unresectable disease.

Duplicate peripheral blood samples were drawn preoperatively, as previously described.[9] Additional samples were drawn on postoperative day 1 and at follow-up visits in the clinic at 6 to 12 months. Blood samples were obtained from arterial catheters or by venipuncture into 2.7-mL vacuum-sealed tubes (BD Vacutainer) containing 3.2% sodium citrate.

Samples were analyzed with ROTEM (Rotem Inc) after recalcification with 20 μL of 0.2 mol/L calcium chloride (star-TEM reagent; Rotem Inc). Three ROTEM assays were performed (INTEM, EXTEM, and FIBTEM). For INTEM, the intrinsic coagulation pathway was activated with partial thromboplastin phospholipids made from rabbit brain and ellagic acid. This provides a global analysis of coagulation. For EXTEM, the extrinsic coagulation pathway was activated by tissue factor from rabbit brain. This also provides a global analysis of coagulation that is largely insensitive to heparin. In the FIBTEM test, the contribution of platelets to whole blood coagulation is inhibited by the platelet-neutralizing reagent cytochalasin D. The FIBTEM test represents only the fibrin component of coagulation.

The ROTEM variables with standard US reference ranges were used in this study. Clot time (CT) represents the time from the start of measurement until initiation of clotting. Clot formation time (CFT) is the time from initiation of clotting until a clot firmness of 20 mm is detected. Alpha is the angle and reflects the rapidity of clot formation. Maximum clot firmness (MCF) represents the quality and strength of the clot. Hypercoagulability is reflected by decreased CT/CFT, increased MCF, and/or increased alpha. Patients were considered hypercoagulable if 1 or more of the 9 ROTEM parameters (CT, CFT, MCF in EXTEM or INTEM, MCF in FIBTEM) were outside the established reference range.

Plasma was extracted from the additional blood sample and stored in aliquots at −70° C. Batched plasma samples were thawed and assayed in the University of Miami/Jackson Memorial Hospital Special Coagulation Laboratory in the Department of Pathology for a panel or hemostasis markers, including quantitative D-dimer, prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen level, protein C activity, protein S activity, prothrombin fragment 1+ 2 antigen, coagulation factor VIII activity, antithrombin III (ATIII) activity, and plasminogen activator inhibitor-1 (PAI-1) activity.

Only patients with baseline, postoperative, and follow-up ROTEM data at least 6 months postoperatively were included. Demographics, operative details, tumor data, symptomatic VTE, and outcomes were collected. Pathology reports were reviewed to determine histologic type and tumor grade. Tumors were staged based on the TNM classification used by the American Joint Committee on Cancer (AJCC).

Data were analyzed with SPSS Ver. 21.0 (IBM Corporation). Independent data were compared with Student's *t*-test. Categorical data were compared using chi-square test or Fisher's exact test. Longitudinal changes in coagulation markers were assessed with repeated measures analysis of variance (ANOVA) and post-hoc comparisons with Bonferroni correction. Values are expressed as mean ± standard deviation. Significance was assessed at $p < 0.05$.

RESULTS

The study population comprised 52 patients (60% male) with no mortalities and a mean (±SD) age of 66 ± 10