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321.COAGULATION AND FIBRINOLYSIS: BASIC AND TRANSLATIONAL

A D-Dimer and Thrombin Generation-Based Risk Score Predicts Early-Disease Recurrence in a Prospective Cohort of 1,059 High-Risk Breast Cancer Patients

Patricia Gomez-Rosas, MD[1,2], Marina Marchetti, PhD[2], Cinzia Giaccherini[2], Laura Russo[2], Cristina Verzeroli[2], Sara Gamba[2], Carmen Julia Tartari, PhD[2], Silvia Bolognini[2], Chiara Ticozzi[2], Francesca Schieppati, MD[2], Luca Barcella, MD[2], Roberta Sarmiento, MD[3], Giovanna Masci, MD[4], Carlo Tondini, MD[5], Fausto Petrelli, MD[6], Francesco Giuliani, MD[7], Andrea D'Alessio, MD[8], Filippo De Braud, MD[9], Armando Santoro, MD[10], Roberto Labianca, MD[11], Giampietro Gasparini, MD[3], Anna Falanga, MD[2,12]

[1] Maastricht University Medical Center (MUMC+), Cardiovascular Research Institute Maastricht (CARIM), Maastricht, Netherlands
[2] Department of Immunohematology and Transfusion Medicine, Hospital Papa Giovanni XXIII, Bergamo, Italy
[3] Oncology Unit, Hospital San Filippo Neri, Rome, Italy
[4] Oncology Unit, IRCCS Humanitas Institute, Rozzano, Italy
[5] Oncology Unit, Hospital Papa Giovanni XXIII, Bergamo, Italy
[6] Oncology Unit, Hospital Treviglio-Caravaggio, Treviglio, Italy
[7] Oncology Unit, IRCCS Cancer Institute Giovanni Paolo II, Bari, Italy
[8] Medical Oncology and Internal Medicine, Policlinico San Marco, Bergamo, Italy
[9] Oncology Unit, IRCCS National Cancer Institute, Milan, Italy
[10] Humanitas Cancer Center, Rozzano, Italy
[11] Fondazione ARTET Onlus, Bergamo, Italy
[12] University of Milano-Bicocca, Monza, Italy

Introduction: Hemostatic biomarkers have been widely explored in different cancer types as possible predictors of specific cancer outcomes, including survival, malignant disease recurrence, and progression. Results from many small and single-center studies are promising, stimulating confirmatory data from large, prospective studies. In a large cohort of high-risk breast cancer patients enrolled in the prospective, observational, multicenter HYPERCAN study, we aim to establish whether prechemotherapy hemostatic levels can predict disease recurrence (DR).
Methods: TheHYPERCAN study (ClinicalTrials.gov ID#NCT02622815) is a prospective, observational, multicenter study, specifically designed to evaluate the role of hemostatic biomarkers in relation to disease recurrence, disease progression, mortality response to therapy and thrombosis. Patients with surgically resected high-risk breast cancer enrolled between 2012 and 2019, from the HYPERCAN study were analyzed. Blood samples collected at enrollment, before starting anticancer treatment, were tested for thrombin generation (TG) by both the ST-Genesia system (STG-ThromboScreen reagent, with and without thrombomodulin) and the calibrated automated thrombogram (CAT) at 5 pM TF. D-dimer, fibrinogen, prothrombin fragment 1+2 (F1+2), and proteins C and free protein S (FPS) were also measured. Outcome analyzed was early-DR (E-DR) within 2 years.
Results: A total of 1,059 patients (15M/1,044F), mean age 53 years (SD±11) were analyzed. Breast conserving-resection was performed in 53% and mastectomy in 47% of patients. HER-2 expression was positive in 26% of tumor specimens. The most frequent molecular subtype was Luminal B HER2 negative (32%), followed by Luminal A (22%), Luminal B HER2 positive (19%), Triple negative (13%) and HER2 positive (8%). The largest proportion of tumors were classified as invasive ductal carcinoma, diagnosed in 86% of subjects. All patients were eligible for systemic adjuvant chemotherapy, and for receiving trastuzumab in case of HER-2 positivity. Within 2 years from enrollment, 53 (5.5 %) patients experienced an E-DR, 8 died, while 92 were lost at follow-up. E-DR patients were characterized by worse stage (IIIC), more frequently triple-negative, and less often Luminal-B/HER2-positive molecular subtypes ($p<0.05$). In addition, E-DR subjects were characterized by increased pre-chemotherapy levels of D-dimer ($p=0.004$), and peak of TG performed by both Genesia ($p=0.001$), with and without thrombomodulin, and by CAT ($p<0.001$) assays. The remaining coagulation parameters were not significantly different between the two groups. The competitive multivariable proportional hazard regression model, corrected for age and surgery status, identified D-dimer and

TG peak (by both methods) as independent risk factors for E-DR. This model was internally validated by 1,000-bootstrapping resampling correction. A continuous risk score was therefore generated including D-dimer and TG, which provided a ROC AUC of 0.652 ($p<0.001$). By this score the patients were significantly stratified in a high- vs low-risk for E-DR (HR 23 vs 0%: Log-rank <0.001).

Conclusions: In this large prospective cohort of surgically resected breast cancer patients at high-risk of DR, we could generate and internally validate a risk assessment model based on pre-treatment values of TG and D-dimer, able to identify those subjects at higher risk of DR in the first 2 years after tumor resection. This score, if externally validated, may help the clinical surveillance and serve as treatment guidance in patients with primary breast cancer that are at high risk of recurrence, avoiding overtreatment in those at low risk.

Disclosures Santoro: *Gilead:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Pfizer:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Eisai:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Celgene (BMS):* Speakers Bureau; *AstraZeneca:* Speakers Bureau; *Servier:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Eli Lilly:* Speakers Bureau; *Incyte:* Consultancy; *Bayer:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Sanofi:* Consultancy; *BMS:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Merck MSD:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Takeda:* Speakers Bureau; *Roche:* Speakers Bureau; *Abbvie:* Speakers Bureau; *Amgen:* Speakers Bureau; *Sandoz:* Speakers Bureau; *Novartis:* Speakers Bureau; *Arqule:* Other.

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