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Editorial

Impact of Chemotherapy in Cancer-Related Venous Thromboembolism. Looking for Prediction

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Cancer patients are characterized by an acquired thrombophilic condition predisposing to increased risk of venous thromboembolism (VTE) [1]. Former studies have probably underestimated VTE incidence, since most of them were retrospectively conducted on patients cohorts recruited before the advent of targeted therapies, or have been focusing only on objectively confirmed symptomatic VTE. Recent research, in fact, pointed out to a higher incidence of VTE in the "real-world setting" than previously reported [2]. This might be related on improvements in computed tomography scanner technology, which has increasingly led to the detection of incidental VTE on scans performed for (re)staging of disease [3] and may have been caused, as well, by the introduction of novel therapeutic approaches with detrimental effects on vascular functions [2].

In this respect, the role played by chemotherapy in cancer-related VTE is unquestionable, and both indirect and direct evidences point out to a strong association between VTE onset and timing or type of anticancer drugs used [4,5]. Indeed, the time course of VTE incidence after an initial cancer diagnosis is highest in the first 3-6 months (i.e. during possible administration of adjuvant chemotherapy), declining during remission at rates similar to those observed in the general population and increasing again at time of relapse and related treatment [6]. However, while the use of thromboprophylaxis in hospitalized patients is currently acknowledged by all major societies' guidelines [7,8], it is still not recommended for ambulatory cancer patients receiving chemotherapy with only few exceptions, mainly represented by patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens or very selected high-risk patients with solid tumors receiving chemotherapy, in whom, according to the latest guidelines issued by the America Society for Clinical Oncology, "*clinicians may consider LMWH prophylaxis on a case-by-case basis ..... Consideration of such therapy should be accompanied by a discussion with the patient about the uncertainty concerning benefits and harms as well as dose and duration of prophylaxis in this setting*" [8].

This latter concept is of particular concern in those segments of the population defined as "fragile", meaning especially the elderly in whom risk and benefit of thromboprophylaxis stands over a particularly uncertain threshold as a result of co-morbidities and impaired cardiovascular function. Cancer, in fact, is becoming an increasingly common problem in elderly patients and the number of older adults seeking treatment for cancer is considerably increasing. The chemotherapyassociated prothrombotic risk associated could find a favourable ground in elderly, who due to the presence of incidental cardiovascular risk factors (hypertension, diabetes, etc..) are more likely to develop thrombotic events [9], which might ultimately impact on active treatment, quality of life and increased demand for health care-related costs.

Hence, the need for stratification techniques to identify high-risk patients who might benefit from thromboprophylaxis. Accordingly, efforts have been devoted to identify candidate biomarkers that may be used in VTE risk assessment [5,10-16]. However, no specific biomarker has been recognized, so far, as a predictor for VTE in cancer out-patients [17]. Indeed, some of them are interesting, but poorly feasible in a general practice setting, as in the case of soluble P-selectin, thrombin generation assays, tissue factor and microparticle measurements, which can not be routinely evaluated, but require second-level test performing laboratories and/or skilled personnel [12-14,16]. Other tests might have a clinical application, such as D-dimer, which has been shown to have a predictive role in cancer-associated VTE [10,11,15], but whose value is still debated due to low accuracy and positive predictive value (PPV), which allow just a limited prediction for an individual patient [18-20]. In this respect, we must acknowledge that a large variety of D-dimer assays are commercially available and that their poor standardization makes impossible direct comparison of results obtained with different D-dimer methods [20]. Overall, the enzyme-linked immunofluorescent assays are considered the goldstandard of D-dimer testing having the highest diagnostic accuracy for

VTE exclusion. Lately, high-sensitive latex quantitative D-dimer assays have become available in the laboratory routine. Using one of such assay, we recently demonstrated that D-dimer testing was capable of predicting a first VTE episode with a PPV twice that reported by other authors, without any substantial loss in negative predictive value or test accuracy [21].

If the type of assay used is crucial, on the other hand, the definition of appropriate cutoffs is not less important. Recent reports, in fact, pointed out to the need to establish different cutoffs for young-middle aged patients or elderly, given that the latter category is characterized by several comorbidities (mainly related to cardiovascular risk) which might interfere with the predictive value of a given biomarker. For that reason, the definition of an age-adjusted cut-off for D-dimer has been proposed to improve VTE diagnostic work-up of older patients with clinically suspected deep venous thrombosis [22].

A final issue that must be addressed is that cancer patients are in a thrombophilic, proinflammatory state, regardless of the presence or absence of VTE clinical evidence and only concurrent risk factors (i.e., antineoplastic treatment) might definitive influence VTE development [23]. Thus, in our opinion, monitoring coagulation changes during the first chemotherapy cycle, more than the determination of a single point measurement at baseline, could provide a valid estimate of the associated pro-thrombotic risk and might help to identify patients susceptible of developing VTE during treatment [5,14]. Beside the search for new biomarkers, other authors have addressed the problem of identifying high-risk patients through the development and validation of clinical risk models. In 2008, Khorana and colleagues developed and validated a formalised risk assessment models for chemotherapyassociated VTE using a scoring systems weighted on the bases of the regression coefficients obtained from a derivation model [24]. This predictive score, assigns 2 points to very high risk (pancreatic or gastric) or 1 point to high risk cancer sites (lung, ovarian or bladder). In addition, 1 point each is assigned for: platelet count >350x109/L, leukocyte count >11x109/L, hemoglobin <10 g/dL (or use of erythropoietin-stimulating agents) and body mass index >35 kg/m2. Simple enough to be used in clinical practice and externally validated by independent groups [11,14,25], the Khorana score correctly assigns patients to the high-risk category, but fails to classify approximately 40% to 60% of patients (intermediate risk), in whom clinical decision making remains challenging. Consistent with these observations, expanded risk scoring models, in which points were added based either on laboratory tests [11] or on platinum-based or gemcitabine chemotherapy [25] were recently proposed. Nonetheless, clinical decision making for thromboprophylaxis in ambulatory cancer patients undergoing chemotherapy remains challenging and might not be justified in particular clusters of patients, such as those identified as “intermediate risk class” using the Khorana’s model, some of which are likely to be in high-risk, and could benefit from prophylaxis.

As discussed above, the development of the Khorana model for cancer-associated thrombosis was based on a multivariate logistic regression model and was, thus, based on a rigorous statistical approach. However, given the wide variety of clinical and laboratory features known to confer an increased VTE risk to cancer patients, we are witnessing a database increase in the number of variables. Accordingly, multifactorial analysis by common biostatistic techniques can be biased by low statistical power due to inadequate sample size even in the presence of large numbers. A second challenge arises from the estimation of chemotherapy effects for an extended period, as these survival outcomes may be estimated with high variability and may be difficult to interpret. This results in an urgent need for new generation of computational theories and tools to assist researchers in extracting knowledge from the growing volumes of data. Open discussion and specifically designed studies are needed to improve risk assessment models which may help identify ambulatory cancer patients who may benefit from outpatient VTE prophylaxis.

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