

## Editorial

 Prognostic Factors for Thrombosis in Cancer Patients<sup>☆</sup>

## Factores predictores de trombosis en pacientes con cáncer

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Jean-Baptiste Bouillard first reported the relationship between cancer and venous thromboembolism (VTE) in 1823, and years later Armand Trousseau identified the association between gastric cancer and VTE. Since then, numerous studies have corroborated this clinical association. Cancer is one of the biggest global public health problems. In Spain, it is the leading cause of death and prevalence is expected to increase due to longer survival of patients resulting from advances in diagnostic and therapeutic procedures. The impact of venous thromboembolism can be devastating; in fact, it is the second leading cause of death after the cancer itself in patients with malignant disease.<sup>1</sup> Moreover, the burden of other consequences, such as the impact on quality of life or severely incapacitating sequelae, including post-thrombotic syndrome of the lower limbs or chronic post-thrombotic pulmonary hypertension, has not been calculated.

The estimated accumulated incidence of VTE presenting as both deep vein thrombosis (DVT) and pulmonary embolism (PE) is between 4% and 20% in all patients with cancer, although its true incidence may be as high as 50%, if findings of thrombosis on autopsy are taken into account. The annual incidence is 0.5%, compared with 0.1% in the general population.<sup>2</sup> The risk of VTE in patients with cancer is higher than in the general population due to several factors: patient-dependent factors, such as age, comorbidities or personal or family history of VTE; tumor-dependent factors, associated with adenocarcinoma histology, site and stage; and treatment-dependent factors, associated with use of central catheters, certain chemotherapy agents, hormone therapy, erythropoietic agents, blood transfusions, periods of hospitalization, and angiogenic agents. Moreover, the risk can increase in the presence of some biomarkers, such as pre-chemotherapy thrombocytosis and leukocytosis, and hemoglobin levels <10 g/dl. The general indication of antithrombotic prophylactic treatment, which can significantly reduce the risk of thrombosis (hazard ratio: 0.36 [95% CI: 0.21–0.60]),<sup>3</sup> is an ineffective approach, because the risk is

distributed unevenly among the global population of patients with cancer, and this intervention increases hemorrhagic complications.

This clinical scenario has led to a search for predictive models of thrombosis in patients with cancer. The most widely used scale and the only one that is validated is the Khorana index, which, curiously, was derived from a registry of patients not designed to construct a set of predictive rules for thrombosis. The Khorana scale is based on clinical and laboratory variables and stratifies patients into 3 risk groups as low, intermediate, and high risk, based on the scores obtained: 0, 1–2 and  $\geq 3$ , respectively. Khorana allocates the highest score (2 points) to cancer of the pancreas or stomach. One point is allocated if the diagnosis is lung cancer, lymphoma, or gynecological, bladder or testicular cancer, if pre-chemotherapy thrombocytosis or leukocytosis are detected, if hemoglobin is <10 g/dl, and if the patient uses erythropoietic agents or has a BMI  $\geq 35$ . Despite its popularity, this index is controversial, and some data suggest that its low positive predictive values undermine its usefulness.<sup>4</sup> In the Vienna CATS Score, two more biomarkers were added to the Khorana index, D dimer (DD) and P-selectin, which increased the probability of thrombosis in high-risk patients by 35%. High P-selectin levels have been detected in the cancer population in general, and probably reflect endothelial activation, which in turn would increase leukocyte recruitment. Even so, the search for clinical and biological markers that can be combined in predictive models to detect the risk of thrombosis in cancer patients remains a challenge in clinical and translational research, and has led to studies that explore the pathobiology of cancer associated with TVE and to new approaches. The ONCOTHROMB<sup>5</sup> study has recently developed a scale that integrates both clinical and genetic factors.

In addition to the most well-known biomarkers, such as DD, P-selectin, leukocytosis, thrombocytosis, soluble tissue factor and endogenous thrombin generation,<sup>6</sup> and other newer biomarkers, such as hypoalbuminemia and Leiden factor V,<sup>7</sup> interest in hypofibrinolysis has been rekindled, since it was observed that raised PAI-1 may contribute to the development of TVE in pancreatic and brain cancer.<sup>8</sup> Promising biomarkers have emerged, such as tissue-factor-bearing microparticles or microvesicles (MPs-TF) and neutrophil extracellular traps (NETs) from cell membrane extracts. To date, there has been a lack of standardization in the determi-

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nation of new biomarkers, in both pre-analytical and analytical conditions. In this respect, our group has helped clarify some of the methodological problems in the measurement of MPs.<sup>9,10</sup>

MPs are elevated in different types of cancer, but the association between MPs-TF and TVE has only been documented to date in cancer of the pancreas.<sup>11</sup> NETs, extracellular DNA networks, and histones released by neutrophils can be detected in tumors, and these NETs play a fundamental role in clot formation; certain indirect parameters of clot formation, such as citrullinated histone H3, have been shown to be possible biomarkers of thrombosis in cancer patients.<sup>12</sup>

Another approach is the study of biomarkers in tumor tissue. The expression of intratumoral podoplanin, a mucin that activates platelets via the CLEC-2 receptor, is associated with VTE in patients with brain cancer<sup>13</sup>; and other studies suggest that differential expressions of mRNA in colon<sup>14</sup> and lung<sup>15</sup> cancer in patients with and without VTE would help to select those most at risk of thrombosis.

Despite so much new information, a lot of work is still to be done: we need predictive models that integrate information about the tumor (site, histology, molecular classification, tumor control, stage, type of chemotherapy used), the patient (age, sex, comorbidities, and history), and the dynamic nature of the clinical presentation, which can be remarkable in cancer patients. In the future, composite scales consisting of multiple biomarkers might be designed that will distinguish between different cancer patients.

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