Editorial

Introduction to a series of reviews on cancer-associated thrombotic disease

Many of the readers of Blood will be responsible, in one context or another, for teaching trainees about the excitement and challenges provided by the discipline of hematology. Within the scope of hematology teaching, it is probably fair to say that the introduction of the coagulation cascade has not usually fared well in terms of student popularity. For many students, this has appeared as an isolated, complex biochemical pathway designed to generate fibrin and result in convoluted exam questions that threaten their grade point average.

However, in recent times, it has become increasingly apparent that the hemostatic system has physiological and pathophysiological associations far beyond the production of a fibrin clot. There is now robust evidence that various components of the hemostatic orchestra play key roles in processes such as inflammation, angiogenesis, cytoprotection, cell proliferation, and apoptosis. Thus, the perhaps previously arcane field of hemostasis is now emerging as a central player in the regulation of many complex human pathologies, is generating interest among subspecialists as diverse as intensivists to obstetricians, and is even finding favor among trainees!

One related discipline for which the association with hemostasis has at least a long-standing historic basis is oncology. In 1823, the French physician Jean-Baptiste Bouillaud (see figure, left) published what appears to be the first report of an association between cancer and thrombosis. This was followed in 1865 by the more widely quoted description by Armand Trousseau (see figure, right) of an association between gastric cancer and venous thrombosis. These reports marked the beginning of a realization that neoplastic disease and hemostasis interact in a complex manner that appears to

Jean-Baptiste Bouillaud (1796-1881) and Armand Trousseau (1801-1867). Professor Bouillaud first reported an association between cancer and thrombosis in a manuscript published in the Archives of General Medicine in 1823. However, it is Professor Trousseau’s report in 1865 that is more widely quoted as the first documentation of this phenomenon. Professor Trousseau was certain of the importance of this association, stating that “So great, in my opinion, is the value of phlegmasia in the cancerous cachexia, that I regard this phlegmasia as a sign of the cancerous diathesis as certain as sanguinolent effusion into the serous cavities.” At the age of 66, he recognized the development of phlebitis in his left upper arm, was soon thereafter diagnosed with pancreatic cancer, and died months later. Portraits courtesy of the National Library of Medicine.

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magnify the adverse outcomes of both processes. Ironically, during the course of his own pancreatic cancer, Professor Trousseau later observed the development of thrombosis in himself.

Cancer patients are at increased risk of venous thromboembolism, one of the leading causes of death in cancer patients. Furthermore, the development of thrombotic disease in a cancer patient is associated with a worse survival outcome.

Although the link between cancer and thrombosis has been recognized clinically for a very long time, it is only recently that the tools of modern molecular science have begun to determine the pathogenetic basis for this propensity and to provide opportunities to improve the clinical management of this disease complex.

The increased incidence of thrombotic disease in patients with cancer spans a wide range of neoplastic disorders, from solid tumors such as carcinoma of the pancreas, stomach, and lung, and brain tumors, to hematologic neoplasms such as myeloproliferative disorders and myeloma. In addition to this wide array of associated tumor types, a growing number of other clinical influences such as advanced age, chemotherapy, hormone therapy, antiangiogenic agents, and central venous catheters further enhance the thrombotic risk in this population.

Given the diversity of cancer types associated with an increased thrombotic risk, it is not surprising that there are a number of different prothrombotic mechanisms that have been characterized as the initiators of the thrombotic process in this clinical setting. Prominent among these mechanisms is the generation of cellular microparticles and the expression of tissue factor on tumor cells and platelets. Other interactions with the hemostatic system involve direct activation of factor X, endothelial activation, and both pro- and antifibrinolytic influences.

Although the incidence of thrombotic disease is unequivocally increased in cancer patients, the magnitude of this enhanced risk is highly variable. Thus, whereas mitigation of the thrombotic risk with prophylactic anticoagulants is warranted for some patients, this intervention is not justified for all. With this in mind, there is now an increasing interest in the development of risk assessment models incorporating clinical parameters and laboratory biomarkers to stratify the thrombotic risk for cancer patients. Evolving evidence suggests that the application of these scoring protocols is clinically advantageous, although important questions remain: there is no clear strategy for determining how long thromboprophylaxis should be maintained, and for some tumor types, such as pancreatic cancer, the thrombotic risk may be high enough to warrant thromboprophylaxis without the consideration of other risk factors.

Finally, in addition to the increased likelihood of thrombotic events in cancer, there is also evidence that certain forms of anticoagulant management are less effective in this setting. This observation has prompted the evaluation of alternative anticoagulant schedules that have the potential to nullify the more pronounced prothrombotic stimulus associated with some neoplasms.

The collection of mini-reviews relating to cancer-associated thrombotic disease that begins in this issue of Blood will present timely summaries of information ranging from the epidemiology of this association to an update of its clinical management (Table 1). I hope you find the series interesting and informative.

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Associate Editor, Blood

Table 1. Mini-review series on cancer-associated thrombotic disease

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