Preface

Cancer-Associated Thrombosis and Beyond: Biomarkers, Treatments, and Cancer-Hemostasis Interactions

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It is firmly established that thromboembolic disease is a common complication of cancer and, overall, venous thromboembolism (VTE) remains the second most common cause of death in cancer patients after the malignancy itself.[1] Besides the direct contribution to cancer-related mortality, cancer-associated thrombosis (CAT) may cause delay or disruption of anticancer treatment. The patient who experiences a cancer-associated VTE will be prescribed anticoagulant treatment, often long-term, which leads to increased number of bleeding events and can be challenging to manage in connection with surgery or antineoplastic agents. Finally, cancer patients report that occurrence of a CAT has a significant negative influence on their quality of life.[2]

The past 20 years have seen increasing focus on CAT from the international scientific community, and great research efforts have been made to elucidate mechanisms behind CAT, to identify new CAT biomarkers and establish reliable CAT risk assessment models, and to develop improved treatment modalities. Traditionally, CAT has been almost synonymous with cancer-related VTE, but it is now recognized that cancer patients also have increased risk of arterial thrombosis.[3] Looking beyond secondary hemostasis, platelets have gained focus as contributors to CAT, both arterial and venous.[4] Conversely, the concept of the hemostatic system as a contributor to the tumor microenvironment and a promoter of cancer growth and metastasis is now established, which has raised questions about the potential for antiplatelet or anticoagulant agents in improving cancer prognosis. Several different CAT risk assessment models have been published, beginning with the Khorana score in 2008,[5] and are being used in research and clinical work, though the optimal strategy for risk stratification and thromboprophylaxis in different inpatient and outpatient settings remains to be determined.[6] The approval of direct oral anticoagulants (DOACs), specifically factor Xa inhibitors, for the treatment of cancer-related VTE has been a great step forward as they offer an effective and safe oral alternative to parenteral low molecular weight heparins for many cancer patients. However, they are associated with a higher bleeding risk in some cancer types, and concerns about interactions with antineoplastic agents have limited their use in cancer patients.

Thus, the current issue of *Seminars in Thrombosis and Hemostasis* (STH) is meant to address some of the current uncertainties in this area. The first paper in this issue takes a closer look at what we sometimes take for granted: the prevalence of thrombosis in cancer. Betts et al performed a network meta-analysis including more than 3,000,000 patients with 18 different cancer types to estimate overall and cancer-specific VTE risk.[7] Overall, 3.1% of the included patients experienced VTE within 1 year of diagnosis, ranging from 0.7% (melanoma) to 7.4% (pancreatic cancer). In the setting of surgery, esophageal cancer had the highest postoperative VTE risk. The review illustrates the differences in VTE rates in different cancer types and settings, and highlights some cancers not previously considered high-risk in all risk assessment models (e.g., myeloma and brain cancer). Moving from VTE to arterial thrombosis, Michel and colleagues give a comprehensive overview of our current knowledge of the mechanisms and risk factors of cancer-associated ischemic stroke and discuss acute and long-term management strategies, keeping in mind the often delicate balance between intracranial thrombosis and bleeding in this patient group.[8] Important focus points for future research are the use of more uniform classification of cancer-associated stroke and improvement of our understanding of mechanisms and risk factors behind cancer-associated stroke.

The next five papers cover CAT biomarkers, each focusing on a specific part of the hemostatic system. A systematic review and meta-analysis by Malte et al investigated platelet parameters as markers for CAT and shows that platelet count is consistently associated with CAT across different cancer types and clinical settings.[9] Platelet count is cheap, fast, and readily available in most hospital laboratories worldwide

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and is included in the Khorana risk assessment model. However, platelet count is influenced by a plethora of other factors. Other markers of platelet reactivity, especially mean platelet volume, which is also available on automated cell counters, or dynamic platelet function assays, not available on automated cell counters, could give more detailed information, but should be investigated in larger cohorts.

Looking at secondary hemostasis, Gyldenholm et al reviews the potential of thrombin generation markers in CAT.[10] The importance of thrombin formation in CAT development is well-established; however, thrombin formation markers are not routinely implemented in diagnostic laboratories. The review by Gyldenholm et al concludes that prothrombin fragment $1+2$ has potential as a CAT risk biomarker while, perhaps surprisingly, ex vivo thrombin generation is less clearly associated with CAT, though also less commonly researched.

From thrombin to fibrin, Ząbczyk and Undas reviews the importance of fibrin clot properties in CAT.[11] Altered clot properties have been described in various cancer types including both hematological and solid tumors, and resistance to lysis has been associated with future VTE risk in multiple myeloma patients. The authors summarize our current knowledge on the mechanisms behind altered clot properties in cancer and the implications for CAT prophylaxis and treatment. Then, Pamulapati et al zoom in on the role of viscoelastic tests in predicting VTE and flap thrombosis, specifically in breast cancer patients undergoing reconstructive surgery.[12] Viscoelastic tests are available in hospital laboratories around the world and, due to their fast turnaround times and global hemostasis assessment, they are theoretically attractive in CAT risk assessment. However, current standard protocols are developed mainly for guiding hemostatic treatment in the face of bleeding, and the potential of viscoelastic tests to detect hypercoagulability and assess thrombosis risk on an individual-patient level is debated. Finally for this group of papers, Elsherif et al summarize available evidence on the influence of ABO blood group on CAT risk.[13] Non-O blood group is a well-known though moderate VTE risk factor in the general population,[14] probably with von Willebrand factor as a key mediator, and current literature indicates that the association between ABO blood type and VTE may be aggravated in cancer patients, probably more strongly in low/intermediate VTE risk cancers.

The different elements of the hemostatic system are then integrated in a comprehensive review on pancreatic duct cancer by Willems et al.[15] As pancreatic cancer has one of the highest incidences of thrombosis among cancer types, it is of interest both as a model for CAT and also as a field with a high potential for absolute risk reduction. Willems et al reviews mechanisms behind CAT in pancreatic cancer and argue that the cellular elements of the blood, including microvesicles, may play a pivotal role in pancreas cancer and should be a focus for future biomarker research and therapy. Wojtukiewicz et al round off this part of the theme issue by asking whether the search for new biomarkers and risk assessment models in cancer is really justified—and whether we are looking in the right direction?[16]

The issue continues with a view on the hemostatic system as not only the basis for CAT but also as a promoter of malignancy. Harvey Roweth, a winner of the 2022 Eberhard Mammen Young Investigator Award,[17] describes the roles of platelets as primers of the premetastatic niche and in consolidating metastatic tumor growth,[18] while Aleksandrowicz et al reviews interactions between thrombin and the immune system in the context of malignancy.[19] These two reviews present and underline the clear evidence that hemostatic activation has tumor-promoting effects. The question is: what are the therapeutic implications? To translate current knowledge into interventions which can improve overall cancer mortality, future research could focus on identifying specific patient groups or settings where antithrombotic therapy could have a positive effect on disease progression and survival.

While systemic chemotherapy is known to be associated with increased thrombosis risk, not much is known about the effect of hyperthermic intraperitoneal chemotherapy (HIPEC) on hemostasis. This treatment is given in adjunction to cytoreductive surgery in patients with peritoneal carcinomatosis and has been shown to improve 5-year mortality[20]; however, HIPEC is possibly associated with an aggravated postoperative VTE risk.[21] The next paper in the present issue by Lundbech et al aims to get behind the potential increased VTE risk in HIPEC and reviews the effect of HIPEC on hemostatic activation.[22] The authors conclude that possible mechanisms behind increased VTE risk are an increased acute response, indicated by increased factor VIII and fibrinogen, and possibly impaired fibrinolysis. HIPEC did not greatly influence standard coagulation markers or platelet count, while dynamic assays of platelet activation, thrombin generation, or fibrin formation have only been sparsely researched. Currently, the optimal thromboprophylaxis strategy for these patients remains to be determined.

The issue is concluded with an extensive work by Hellfritzsch et al evaluating possible interactions between DOACs and antineoplastic agents.[23] This has been a concern with many CAT patients and their caregivers. Unfortunately, there are not many in vivo interaction studies in this field, and therefore some guidelines have recommended a cautious approach.[24] Hellfritzsch et al collected extensive information on pharmacokinetic properties and the available evidence of drug–drug interactions for 100 antineoplastic agents and the four DOACs dabigatran etexilate, rivaroxaban, apixaban, and edoxaban. They then develop a framework for assessing the likelihood of drug–drug interactions and show convincing evidence that most antineoplastic agents can be safely combined with at least one DOAC. This important work will certainly support future decision-making when choosing CAT treatment.

In summary, with this STH theme issue, we aim to update the readers on a wide range of topics relevant for cancer patients, researchers, and clinicians, including an update on site-specific CAT prevalence, detailed summaries of hemostasis biomarkers and risk assessment models in CAT, and the newest evidence of hemostatic factors as tumor promoters. We hope you will enjoy the reading!

Finally, since this issue is publishing in 2024, and STH is celebrating 50 years of publishing in this year, this issue

contains a bonus of a manuscript republished from the archives,[25,26] and an associated Commentary.[27] The historical manuscript represents the second most cited publication from STH of all time.[28]

Conflict of Interest
None declared.

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