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REVIEW ARTICLE

Thrombotic complications in patients with cancer: Advances in pathogenesis, prevention, and treatment—A report from ICTHIC 2021

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Abstract

Venous thromboembolism (VTE) is a common complication in cancer patients, resulting in deep vein thrombosis (DVT) or pulmonary embolism (PE), and is responsible for high morbidity and mortality. This article discusses evidence and future perspectives on pathogenesis and prevention and treatment of thrombotic complications in patients with cancer. In April 2021, international basic researchers and clinicians met for the virtual edition of the 10th International Conference on Thrombosis & Hemostasis Issues in Cancer. Pathogenic mechanisms, markers and scores for risk assessment, diagnosis and therapy issues, current prophylaxis recommendations, and special settings, such as palliative care, pediatrics, and COVID-19 patients were discussed. Emerging areas of interest in cancer associated VTE are the role of immunotherapy, platelet activation markers, genetic alterations and real-world systems-based approaches to prevention and treatment.

KEYWORDS
cancer-associated thrombosis, coagulation, hemostasis, risk factor, venous thromboembolism

Essentials

- Alterations of the coagulation are responsible for complications in patients with cancer.
- International researchers and clinicians met to discuss advances in this field.
- Assessment of risk, prevention and therapy were discussed.
- Awareness of the problem is high and research is providing tools.

1 | INTRODUCTION

Venous thromboembolism (VTE) is a common complication in cancer patients, resulting in deep vein thrombosis (DVT) or pulmonary embolism (PE), and is responsible for high morbidity and mortality. In April 2021, international basic researchers and clinicians met for the virtual edition of the 10th International Conference on Thrombosis & Hemostasis Issues in Cancer to discuss recent evidence and future

perspectives on pathogenesis and prevention and treatment of thrombotic complications in patients with cancer.

2 | MARKERS OF THROMBOSIS-ASSOCIATED CANCER

Cancer patients have a high frequency of hemostatic disorders ranging from asymptomatic laboratory changes to massive thromboembolism or hemorrhage. Occult cancer estimates vary, but it is detected in approximately 5% of patients with unprovoked VTE in the 12 months following diagnosis.[1] Consequently, circulating factors have been investigated as possible markers of cancer-associated VTE and cancer outcomes, including cancer recurrence, progression, and mortality. Indeed, hemostatic factors have been found to be possible predictors of increased risk for cancer or as markers for early diagnosis.[2]

Currently, D-dimer is routinely measured to exclude VTE. Nevertheless, a low level of D-dimer (<1000 ng/ml) in patients diagnosed with DVT is negatively associated with malignancy.[3] In outpatients with DVT, cancer prevalence is 32% in the group with D-dimer level >4000 ng/ml and 16% in patients with lower D-dimer level ($p = 0.009$, relative risk = 2.0).[4] In addition, an increased incidence of malignancy has been observed in subjects with thrombosis with D-dimer >8 mg/ml at presentation compared with those with lower levels.[5] D-dimer levels >4000 ng/ml are also independently associated with occult metastatic cancer compared with D-dimer <2000 ng/ml.[6] Finally, D-dimer levels have been found to be independently associated with active cancer in ischemic stroke patients admitted to the stroke unit and included as a risk factor in the predictive score for cancer in patients with stroke and younger than 75 years, in addition to other risk factors, such as hemoglobin level, previous smoking, and undetermined etiology.[7,8] In conclusion, current evidence suggests that the dosage of D-dimer, which is a routine test, may be helpful to identify subjects at risk of present or incident cancer.

The cohort observational PLATO-VTE study is investigating the sensitivity of novel biomarkers for cancer detection compared with limited cancer screening in patients with unprovoked VTE.[9] This study uses the multiplexed targeted proteomic assay developed by Mohammed et al. to assess coagulation factor concentrations and thrombosis-associated cancer.[10]

Finally, evidence indicates that increased thrombotic marker levels may be associated with a higher prevalence of occult cancer in the absence of thromboembolism. For example, plasminogen activator inhibitor-1 levels have been positively correlated with an increased risk of colorectal cancer and breast cancer,[11] and high TPA levels have been significantly associated with an increased risk of breast cancer.[12]

The clinical relevance of such findings needs to be demonstrated, and the efficiency of screening programs based on biomarkers is debated. The identification of efficient screening strategies for the early diagnosis of malignancies in patients with VTE requires three steps: "tools" that will predict an increased likelihood of occult malignancy in patients with unprovoked VTE, validation that the these screening strategies will identify at least some subpopulations in which early detection may favorably affect morbidity-mortality, and cost-effectiveness of the proposed programs. Limited programs may encompass routine examinations, such as history, physical examination, basic blood work, and chest radiograph. In contrast, demanding strategies include novel imaging techniques and biomarkers, with relevant differences in cost and organization needs.[13,14]

In 2017, a meta-analysis evaluated screening efficiency for early cancer in subjects with unprovoked VTE. An increased overall prevalence of cancer (5.2% in 12 months and 1.1% in 24 months) was found, but improved survival, cancer-related morbidity, or quality of life did not result from screening.[1] Carrier et al., in a randomized prospective study, found no significant benefit of adding contrast computed tomography of the abdomen and pelvis to routine tests in patients with unprovoked VTE.[15] Robin et al. found that a strategy including limited screening (physical examination, usual laboratory tests, and basic radiographs) and an ^{18}F-flourine-18 positron emission tomography-computed tomography was not associated with a significantly higher rate of cancer diagnosis after unprovoked VTE in comparison with the limited screening only.[16] Such findings suggest that further research is necessary to set efficient screening programs.

3 | NEW INSIGHTS INTO PATHOGENIC MECHANISMS

3.1 | Genetic and epigenetic regulation of the cancer coagulome

The expression of coagulation/fibrinolysis genes across different primary tumor types, the so-called coagulome, depends on cancer cell interactions with their vascular microenvironment and epigenetic transforming events. Some oncogenic mutations, such as *STK11/LKB1*, *KEAP1*, *MET*, *CTNNB1*, *CDKN2B*, and *KRAS*, are associated with an increased risk of thrombosis.[17] Cancer cells, in comparison with normal cells, may have altered expression of mediators of cancer-associated thromboembolism, such as tissue factor (TF/F3) and podoplanin, and other factors (poly-phosphate chromatin, endothelial cell protein C receptor, proteinase-activated receptor 1-2 [PAR1-2], factor VII [FVII], FVIII, plasminogen activator inhibitor-1, urokinase-type plasminogen activator, urokinase-type plasminogen activator receptor, inflammatory cells, neutrophil extracellular traps). Glioblastoma cell populations with distinct oncogenic programs release podoplanin as procoagulant extracellular vesicles, and podoplanin expression in primary brain tumors induces platelet aggregation and increased risk of thromboembolism.[18,19] The study of coagulome provides the opportunity to understand the communication between blood vessels and predict thrombotic complications.

3.2 | Coagulation signaling and cancer immunotherapy

Recent studies have investigated the cell signaling pathways involved in the procoagulant activity of tumor cells. The TF pathway serves both hemostasis and cell signaling. PAR2, which plays a pivotal role in angiogenesis and tumor development, may be activated directly by the TF/FVIIa complex and indirectly by TF/FVIIa-generated activated FX. An integrin-binding site required for proangiogenic signaling has been identified on coagulation FVIIa, independent of the procoagulant activity.[20,21] FX produced in the tumor microenvironment is a regulator of immune cell activation, and this finding suggests that direct oral anticoagulants may promote immunotherapy. Indeed, myeloid cell-derived FX plays a pivotal role in promoting tumor immune evasion. The inhibition of activated factor X contributes to macrophage polarization and regulates tumor progression through FX–PAR2 pathway signaling, thus synergizing with anti-programmed cell death ligand 1.[22] The interplay between tumor cells and coagulation factors affects tumor progression and tumor treatment outcomes.

4 | RISK ASSESSMENT FOR CANCER-ASSOCIATED THROMBOSIS

A survey published in 2020 showed that many oncologists do not talk to their patients about the risk of thrombosis and that most of them are not familiar with the Khorana score, suggesting that this issue is not adequately managed in routine practice.[23] Therefore, clinicians need to become familiar with available diagnostic and prognostic tools.

Indeed, researchers are focusing on more efficient prediction tools than the Khorana score. Several studies have recently suggested factors that may be candidates to be demonstrated as risk factors. Risk factors for developing VTE in cancer patients may be related to the patient (e.g., thrombophilia, comorbidities, performance status, history of venous diseases), the tumor (e.g., cancer site, stage, grade), and the treatment (e.g., surgery, chemotherapy, anti-angiogenesis, hormonal and supportive treatment). Further predictive markers, evaluated before chemotherapy, are blood count parameters (e.g., platelets, leukocytes), and biomarkers (e.g., soluble P-selectin, D-dimer).[24] The relative risk (RR) for VTE in cancer patients is found to be 13.97 (95% confidence interval [CI] 8.28–23.55) for women and 14.60 (95% CI 8.64–24.68) for men.[25] The RR increases over each 10-year increase in age. A higher risk of VTE is associated with some tumor types, such as gastrointestinal tumors, respiratory tumors, and sarcomas.[25] Preliminary data from the still-ongoing observational Vienna Cancer and Thrombosis Study has shown that VTE risk in patients with active cancer is higher for pancreatic tumors and lower for kidney, prostate, and lung cancer.[26]

Recently, patients with cancer under immune checkpoint inhibitor therapy have been found to be at high risk of thromboembolism, especially VTE, and the occurrence of VTE in these patients has been associated with increased mortality.[27] The use of anti-vascular endothelial growth factor (VEGF) agents in advanced non-small cell lung carcinoma (NSCLC) has significantly increased the risk of high-grade arterial thromboembolism but not VTE.[28] Several mechanisms may be involved, such as endothelial cell activation, potentially releasing very high amounts of von Willebrand factor (VWF), including high molecular weight multimer VWF and high consumption of ADAMTS13 metalloprotease, leading to increased platelet-vessel wall interaction. Platelets seem to play a central role in microthrombosis, leading to hemolysis and organ failure. Increased VWF and decreased ADAMTS13 activity have been associated with poor prognosis in patients with advanced NSCLC.[29]

4.1 | Assessment scores for VTE risk

Because individual risk factors cannot identify a sufficiently high-risk group of outpatients for thromboprophylaxis, a simple model for predicting chemotherapy-associated VTE has been developed using baseline clinical and laboratory variables.[30] Based on this score, a clinical prediction model, including tumor size and D-dimer level as variables, has been developed to enable a personalized risk prediction of VTE.[26]

The predictive value of the Khorana score is not equally reliable in all tumors; for example, it only modestly predicts VTE in multiple myeloma patients.[31] For this reason, two new scores have been proposed: the Modified Khorana Score and the CATS Score, which was validated in the SVERT trial.[9,32,33] Specific models have been proposed for certain tumor types, such as the Thrombosis–Lymphoma predictive score for lymphoma patients.[34] Based on five risk factors, the SAVED score predicts VTE risk in multiple myeloma patients on immunomodulatory drug therapy.[35] The IMPEDE VTE Score predicts VTE in newly diagnosed multiple myeloma based on immunomodulatory drug use, body mass index, use of doxorubicin, history of VTE, pelvic, hip, or femur fractures, and current thromboprophylaxis.[36] Nevertheless, VTE risk assessment for cancer patients is not as efficient as needed in clinical practice; more reliable scores should be designed, awareness in the oncologic community should be increased, and further studies should investigate mortality. If direct oral anticoagulants (DOACs) were available in this indication, clinicians might be more likely to use anticoagulation to prevent and treat thromboembolism in cancer patients.

5 | BIOMARKER ASSESSMENT

Preanalytical factors, such as patient identification, sample collection, transport, and processing, may affect coagulation testing and influence some biomarker levels. These factors are responsible for most laboratory errors.[37] In addition, biomarker levels may change according to patient factors, such as age, blood group, sex,

race, pregnancy, and circadian rhythms. Cancer stage, biology, and chemotherapy may also induce variability in biomarker assessment. Standardization of preclinical conditions and methodologies for collecting specimens for each biomarker will improve the reproducibility of tests. Heterogeneity in thrombosis risk and biomarker expression is related to tumor type and tumor burden, and all these variables should be considered. Improved reproducibility could lead to better prediction models using additional biomarkers, including tumor-associated genes and proteins.

6 | THROMBOPROPHYLAXIS

VTE incidence is high during hospitalization in cancer patients, and current international guidelines recommend thromboprophylaxis in this setting.[38,39] At the same time, data are inadequate to support routine thromboprophylaxis in patients admitted for minor procedures or short chemotherapy infusions.[38,40,41] Because evidence of benefit from this practice is still lacking, a pilot study has evaluated the effects of weight-adjusted low molecular weight heparin (LMWH) for hospitalized cancer patients. This intervention was safe, but efficacy demonstration would need further investigation.[42] The incidence of VTE associated with cancer has increased in the past decade because of novel cancer therapies, high-resolution imaging, and improved survival.[43] The benefit of thromboprophylaxis in unselected outpatients with solid tumors was demonstrated with nadroparin compared with placebo in the PROTECHT study[44] and with semuloparin in the SAVE-ONCO study.[45] Because VTE risk is related to the tumor type,[46] the CONKO 004 study has evaluated the benefits of thromboprophylaxis in patients with advanced pancreatic cancer who are at high risk. Enoxaparin-treated subjects had a lower incidence of VTE (6.4% vs 15.1% in controls; hazard ratio, 0.40; 95% CI 0.19–0.83; $p = 0.01$) without interference with chemotherapy or increased risk of bleeding compared with untreated patients.[47] A reduced cumulative probability of VTE was also observed in patients with inoperable or metastatic advanced pancreatic cancer treated with gemcitabine when weight-adjusted dalteparin was used.[48]

7 | TREATMENT OF VTE IN CANCER

Several clinical studies found that anticoagulation in cancer patients was safe and identified preferred strategies and, in the real-life setting, similar rates of VTE recurrence and bleeding occurred with apixaban, LMWH, and warfarin in patients with cancer.[49] Over the past 15 years, guidelines for the management of cancer-associated thrombosis have been published by several international societies, but the effort is needed to improve dissemination, implementation, and adherence.[38,41,50,51] Guidelines are based on recent clinical trials investigating the risk/benefit balance of antithrombotic therapy. The CATCH study found that treatment with tinzaparin was associated with a lower rate of clinically relevant nonmajor bleeding than warfarin therapy. However, a composite of VTE recurrences, overall mortality, and major bleeding was not different in the two groups.[52] The international, multicenter, observational GARFIELD study confirmed the high association of VTE with cancer, the high mortality in cancer patients because of VTE, and the current frequent use of DOACs in cancer patients.[53]

Currently, the choice of dose and duration of anticoagulant therapy for cancer patients is not well defined and cannot be based only on risk stratification for recurrence.[54–56] The risks of thromboembolic recurrence, major bleeding, and mortality during anticoagulant treatment differ according to the cancer site.[57] The similar timing of thrombotic events related to tumor stage and progression can be helpful in better selecting treatment.[58] In addition, the approach may differ according to the type of cancer and the type of thrombotic events.

At present, the predictive value of scores and biomarkers is limited. Personalized medicine based on genetics may provide more reliable markers. Recently, the NSCLC ALK rearrangement has been associated with a VTE recurrence rate of 16%.[59]

The recent introduction of antiangiogenic agents in cancer therapy has generated a new problem for anticoagulation because of the increased risk of bleeding. The main mechanism of bleeding is the disruption of the tumor vasculature by inhibiting VEGF signaling.[60] Most trials on antiangiogenic drugs have excluded patients with thrombosis, but anticoagulation therapy concurrent with bevacizumab was safe in three large trials on patients with colorectal cancer or advanced NSCLC.[61]

Anticoagulation strategies need to consider gastrointestinal absorption, which may be impaired in cancer patients because surgery, nausea and vomiting, and possible drug–drug interactions. This latter problem has been little investigated, but the Caravaggio trial found no interaction between apixaban and anticancer therapies, including supportive care drugs.[62]

7.1 | Improving VTE treatments in palliative care patients

VTE treatment and prevention are challenging in cancer patients hospitalized in palliative care units. Although their risk of VTE is very high, limited evidence is available because these subjects are not represented in clinical trials (exclusion criteria, such as ECOG >2, prognosis <3 months, a weight <40 kg, and altered biochemistry, are all parameters that characterize palliative care patients). To date, some data have been obtained from observational studies. The RHESO study, a multicenter observational study that enrolled 1199 patients in the real-life setting of hospital palliative care, some of which were affected by cancer, found a clinically relevant bleeding rate of 9.8%. Researchers concluded that thromboprophylaxis should be used until death, but the high risk of bleeding should be taken into account when considering anticoagulation.[63] Later, the HIDDen study enrolled 343 cancer patients admitted to palliative care units and showed that VTE was a manifestation of advanced disease rather than a cause of premature death.[64] Therefore, further

research is needed to understand whether thromboprophylaxis is beneficial in this setting.

8 | FOCUS ON THROMBOSIS IN THE PEDIATRIC SETTING

Although VTE is rare in children in the general population (0.06/1000 patient-years), the absolute rate in pediatric cancer patients is 1.52/1000 patient-years, more linked to hematological malignancies than solid tumors.[65–69] Different risk factors have been identified, such as inherited genetic thrombophilia, tumor mass compression, surgery, central venous line, and chemotherapy.[66,70] Indeed, thromboembolism is a known complication of L-asparaginase (ASP) therapy in acute lymphoblastic leukemia (ALL).

Most recommendations for managing thromboembolism in children with malignancies are based on expert opinion because clinical studies have excluded this population. Briefly, the suggested treatment for DVT associated with cancer in children is 3 months of anticoagulation, followed by 6 months of therapy if no clot resolution occurs. Prophylaxis should be continued as long as any of the following risk factors exist: active cancer, central venous line, and chemotherapy. ALL patients who have suffered from DVT when reintroduced to ASP should receive anticoagulant prophylaxis before administration and 48 h after ASP exposure. Primary VTE prophylaxis in children with ALL at high risk should be considered.[66,71,72] LMWH represents the most commonly used drug to treat children with DVT, and VTE prophylaxis is suggested for high-risk ALL patients.

In contrast, DOAC use in pediatric patients, especially those with active cancer-associated DVT, is still limited.[73–75] Only recently, rivaroxaban has been registered for pediatric use in the United States and Europe based on results from the EINSTEIN-Jr study.[76] The body weight-adjusted pediatric rivaroxaban dosing regimens successfully targeted the adult rivaroxaban exposure range without requiring laboratory monitoring. Compared with standard therapy, treatment was safe and resulted in a similarly low risk of recurrent VTE and clinically relevant bleeding. Further clinical studies are expected to optimize the use of DOACs in children.

9 | CONCLUSION

In the past 20 years, the prevalence of VTE in cancer patients has increased. Circulating biomarkers that may predict occult cancer-associated venous thromboembolism and specific cancer outcomes have been investigated, including disease recurrence, progression, and mortality. Risk assessment scores, such as the Khorana score, help clinicians predict VTE onset in cancer patients. The VTE risk is related to tumor-specific sites and cancer treatment. Treatment of VTE may require specific approaches based on cancer type, tumor site, cancer progression, and type of thrombotic event. Thromboprophylaxis is suggested for cancer patients, particularly when hospitalized, because hospitalization remains a major contributor to VTE and 50% of all VTEs are hospital related. Because of the lack of evidence, therapeutic approaches for palliative care patients are limited as available data come from observational studies.

Most evidence about prophylaxis and treatment of VTE in children with cancer is based on adult studies. The use of prophylactic anticoagulant therapy can be considered in selected cases. A DOAC has recently been registered for pediatric use in the United States and Europe, and its role needs to be further evaluated in international multicenter studies.

New emerging trends in the areas of cancer and thrombosis should be explored in future research. The association of new anticancer approaches (e.g., immunotherapy) and VTE and the evaluation of platelet activation markers (e.g., P-selectin) as emerging targets for cancer treatment are of particular interest. Genetic alterations in cancer are increasingly being studied in the clinic to identify targeted approaches and tailor treatment regimens. New research should focus on real-world, systems-based approaches to prevention and treatment, highlighting the often-overlooked aspect of implementation science. Finally, research on cardio-oncological complications is an ever-growing area that should be expanded.

AUTHOR CONTRIBUTIONS

All authors equally contributed to the drafting, reviewing and approval of the manuscript.

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