Editorial Commentary

Is it time for a specific score for venous thromboembolism risk assessment for non-solid tumors?

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Cancer patients have a high incidence of venous thromboembolism (VTE), VTE recurrence, bleeding and reduced quality of life (1). Thrombosis is the second most common cause of death in cancer patients (2). VTE prophylaxis is not routinely recommended for all outpatients with cancer undergoing chemotherapy.

Lymphoma patients are at a higher risk of VTE, compared to different cancer types, particularly with solid tumors (3). The evaluation of thrombosis risk to guide VTE prophylaxis strategies is recommended for patients with newly diagnosed neoplastic diseases. Khorana *et al.* developed a prospectively validated risk assessment tool for predicting chemotherapy-associated VTE. However, in this cohort study, only a minority of patients (12.6%) had lymphomas (4).

Most of the available risk assessment tools are not specific for hematological tumors. Recently the Khorana score was used as an inclusion criterion (≥2) for two prospective, randomized controlled trials in VTE prevention in out-of-patient cancer patients receiving chemotherapy. The Cassini trial (5) compared rivaroxaban 10 mg once-daily versus placebo and the AVERT trial (6) compared apixaban 2.5 mg twice-daily to placebo as well. Both studies showed reductions around 60% of thrombotic events, with a slight increase of bleeding on the apixaban study. The Cassini trial included around 7% of lymphoma patients where the AVERT trial included only solid tumors. Subgroup analysis of these 2 trials are not possible comparing solid versus hematological tumors, and these are currently the largest studies in this setting. *Table 1* describes the currently available VTE risk tools and its features.

VTE prophylaxis and treatment in patients with hematologic malignancies is challenging, particularly because severe thrombocytopenia can complicate the course of treatments or may exist since early diagnosis, increasing the chances of bleeding complications (13). The identification of patients with lymphomas who are at high risk of VTE are warranted to identify who might benefit from prophylactic anticoagulation strategies and those who will benefit from avoiding anticoagulation, preventing bleeding (3). We believe that a specific score to evaluate VTE risk assessment in hematological cancers should be developed and prospectively validated. Such score would include on top of the Khorana risk score, previous history of VTE, disease stage, potential pro-thrombotic associated treatments and biomarkers.

Recently, Borchmann *et al.* (14) evaluated thrombotic events in more than 5,000 patients from the GHSG HD13–15 trials in patients with Hodgkin lymphoma (HL). They have found an overall incidence of thrombosis of 3.3%. The authors reported an incidence of less than 1% events in early-favorable, 1.3% in early-unfavorable and 7.3% in advanced patients, the latter incidence being significantly higher (P<0.001). The majority of the events

Table 1 Currently available VTE risk tools for cancer patients

Score	Types of cancer*	Variables	% hematologic tumors
Khorana *et al*. (4)	Breast, colorectal, lung, gynecologic, gastric, pancreatic and lymphoma	Site of tumor, pre-chemotherapy platelet count, hemoglobin level or use of red cell growth factors, pre-chemo leukocyte count and BMI	13%
Pabinger *et al*. (7)	Breast, prostate, lung, colorectal, oesophagus, kidney, lymphoma, bladder or urothelial, uterus, cervical, ovarian, sarcoma, testicular germ-cell tumors, pancreas and stomach	Site of tumor and D-Dimer	17%
Tic-ONCO (8)	Solid tumors (colon, pancreas, stomach, lung and oesophagus)	Genetic risk score, BMI, family history of VTE, tumor site and stage	0%
COMPASS-CAT (9)	Solid tumors (breast, colon, lung and ovarian cancer)	Type of chemotherapy (anthracycline or anti-hormonal therapy), time since cancer diagnosis, presence of central venous catheter, stage of cancer, presence of cardiovascular risk factors, recent hospitalization for acute medical illness, personal history of VTE, and platelet count.	0%
ONKOTEV (10)	Breast, gastroenteropancreatic genito/urinary tract, lung, kidney, neuroendocrine tumors, head and neck, sarcoma, GIST, hepatocellular carcinoma, skin, brain	Khorana score >2, metastatic disease, previous VTE and vascular/lymphatic macroscopic compression	0%
PROTECHT (11)	Gastrointestinal, lung, breast, ovarian, pancreas, head and neck	Khorana score removing BMI and adding platinum or gemcitabine-based chemotherapy	0%
VIENNA (12)	Breast, lung, stomach, colorectal, pancreas, kidney, prostate, brain (high-grade glioma) lymphoma, multiple myeloma	All variables included in Khorana score + 2 biomarkers: soluble P-selectin, and D-Dimer	Lymphoma (11.8%); multiple myeloma (2.2%)

*, population in the original publication. VTE, venous thromboembolism; GIST, gastrointestinal stromal tumors; BMI, body mass index.

were deep-venous thrombosis (DVT), and 7.8% arterial thrombosis. Interestingly, the majority of events occurred in the upper extremity (46.3%), mainly catheter associated thrombosis. In 24.6% of the patients, VTE occurred in the lower extremities. In advanced HL, the incidence of VTE events was increased upon more intensive treatment with BEACOPP-14. Applying the Khorana score, only age and smoking correlated with the development of VTE.

The authors concluded that the incidence of VTE in advanced stage HL is comparable to other high-risk cancer patients, with a higher incidence in patients that received dose-dense regimens. This study adds important data regarding incidence of thrombotic events and risk factors for VTE in patients with lymphoma. Previous studies in patients with hematologic malignancies have shown similar results (15). Patients with aggressive non-Hodgkin lymphoma (NHL) and advanced stage disease (III/IV), are also at a high risk to develop VTE. A recent retrospective single center study carried out by Hohaus and collaborators evaluated the occurrence of VTE and identified proposed lymphoma-specific risk factors. It was identified 3 specifics clinical risk factors: central nervous system (CNS) lesions, tumor bulk greater than 10 cm and reduced performance ECOG status. This group proposed that VTE risk factors in patients with lymphoma are not the same VTE risk factors described for patients with solid tumors (3).

As for study design, Borchmann *et al.* excluded patients over 60 years old and follow-up was limited to 1 year. We believe that future prospective trials involving patients with individual types of cancer, elderly and with longer follow-up periods would provide the definitive evidence about the clinical benefit associated with prophylaxis in out-of-

hospital patients, particularly in patients suffering from non-solid tumors.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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