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Prevention and treatment of venous thromboembolism in patients with hematological neoplasms

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Abstract

Venous thromboembolism (VTE) risk-assessment models are not always useful in predicting VTE risk in patients with hematological neoplasms. Newly updated guidelines recommend primary prevention of VTE in selected patients with cancer using Khorana Risk Score points. The decision to use anticoagulants for primary prophylaxis should be individualized, taking into account the risk of VTE as well as the risk of bleeding. Randomized trials with direct oral anticoagulants (DOACs) have confirmed their safety, good treatment tolerance, and efficacy in both cancer-associated thrombosis (CAT) primary prevention and CAT treatment in cancer patients. In all clinical trials, patients with hematological malignancies have been underrepresented. Individualized use of DOACs for primary thromboprophylaxis should be based on a patient risk/benefit assessment including thrombocytopenia and drug interactions. Although rivaroxaban or apixaban are safe and efficacious for VTE treatment compared to low-molecular-weight heparin, the choice of optimal anticoagulation in patients with hematological malignancies should be individualized and based on the type of malignancy, the bleeding risks, the concomitant medications, and patient preferences. Further research on primary prophylaxis is required, especially in patients with hematological malignancies.

Key words: venous thromboembolism (VTE), cancer-associated thrombosis, hematological neoplasms, DOACs, VTE prophylaxis, VTE treatment

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Introduction

Patients with cancer including hematological neoplasms have a significant risk of developing a venous thromboembolism (VTE) [1, 2]. Overall, patients with cancer have a four-fold to seven-fold higher risk of cancer-associated thrombosis (CAT) than do patients without cancer [1]. Symptomatic VTE occurs in approximately 10–15% of *de novo* diagnosed patients with hematological malignancies [3]. VTE and arterial thrombosis account for 9% of deaths, aggravate the clinical course of the disease, and worsen the survival prognosis; they constitute the leading causes of death [4]. It has been estimated that patients with CAT have a tripled morbidity [5]. CAT also prolongs hospitalization by up to three times [6]. Various factors can have an influence on the risk of VTE in patients with cancer, and these can be categorized into four main groups: patient-related risk factors (e.g. comorbidities or hereditary risk factors); cancer-related risk factors (e.g. site of cancer); cancer treatment-related risk factors (e.g. selected anticancer or supportive therapy such as thalidomide or erythropoiesis-stimulating agents); and biomarkers (e.g. D-dimer levels). See Table I [6, 7]. The risk of VTE development is also higher in the course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [8, 9].

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Table I. Risk factors for cancer-associated thrombosis (CAT) in patients undergoing treatment for hematological malignancies

Patient-related risk factor	Treatment-related risk factor
Age	Hospitalization and immobility
Comorbidities	Surgery
Prior VTE	Systemic therapy/anti-angiogenic agents/platinum-based regimen/anthracycline-containing therapy
Hereditary risk factors (e.g. factor V Leiden)	Central venous catheters
Presence of varicose veins	ESA/blood transfusion
	Hormonal therapy
Cancer-related risk factor	**Biomarker**
Site of cancer — lymphoma high risk	Hematologic biomarkers (e.g. platelets, hemoglobin, leukocyte counts)
Primary site — CNS	D-dimers
Histology	P-selectin
Grade	Tissue factor-positive microvesicles
Stage	Elevation in plasminogen activator inhibitor 1
Initial period	Others

VTE — venous thromboembolism; ESA — erythropoiesis-stimulating agents; CNS — central nervous system

Several hematological neoplasms and/or location of neoplasms are considered to be high risks of VTE occurrence [10–13]. It has been documented that the risk of thrombosis in patients with lymphoma is similar to patients with solid tumors. Although lymphomas belong to one of the most heterogeneous group of neoplasms, in patients treated for lymphoma the incidence of VTE is 7–15%. But in patients with central nervous system (CNS) lymphoma, the incidence of VTE can be up to 60% [14]. Moreover, novel therapies such as chimeric antigen receptor (CAR) T-cell can lead to coagulopathy and increase the risk of thrombosis [15, 16]. Patients with cancer are not only at increased risk of VTE, but also have an increased risk of major bleeding [17–19]. That is why any consideration of thromboprophylaxis or treatment for patients with cancer should be based on an assessment of the patient's individual risk for thrombosis and major bleeding, after full exploration of the potential benefits and risks.

Prediction models

Several laboratory biomarkers for VTE prediction have been identified [20, 21], including in patients with hematological malignancies [17, 22, 23]. Based on selected biomarkers, several VTE-risk-assessment models in ambulatory patients with cancer have been proposed [24]. The most common for cancer patients is the Khorana Risk Score (KRS; *see* Table II) [25]. A meta-analysis of 34,555 patients with cancer showed that CAT occurs in 10% of patients with cancer within six months, with high risk defined as a score of more than 2 points [26]. In recent clinical guidelines [27–31], thromboprophylaxis should be considered in selected ambulatory patients with cancer and with a high Khorana score (2 or more points) but with a low risk of major bleeding and without drug–drug interactions. In patients with cancer who are starting chemotherapy, primary prophylaxis with apixaban (2.5 mg twice daily) or rivaroxaban (10 mg once daily) or low-molecular-weight heparin (LMWH; in cases of a high risk of bleeding) is recommended. The KRS has been evaluated in patients with lymphoid malignancies, but did not adequately stratify or predict VTE events in patients at a higher risk of VTE [32]. This finding suggests the need for the development of a disease-specific VTE assessment model. For patients with lymphoma, Antic et al. developed and validated a multivariable model for thromboembolic events in lymphoma patients known as the Thrombosis Lymphoma (ThroLy) Score, *see* Table III [33]. The association of ThroLy with VTE in patients treated for diffuse large B-cell lymphoma (DLBCL) or Hodgkin lymphoma (HL) undergoing ambulatory first-line chemotherapy did not show improved prediction of VTE events because 48% of VTE events occurred in the low-risk ThroLy Score group [34].

Assessment of bleeding risk

Overall, in patients with neoplasms, the rate of bleeding complications is higher than in non-cancer patients, ranging from 7% to 33% [18, 35].

Table II. Khorana Risk Score

Characteristic	Score
Site of cancer Lymphoma — high risk	1
Platelet count ≥350 ×10^9/L	1
Hb <10 g/dL or use of ESA	1
Leukocyte count >11 ×10^9/L	1
BMI ≥35 kg/m^2	1
Risk category	
High-risk group: ≥3 points	
Intermediate-risk group: 1–2 points	

Hb — hemoglobin; ESA — erythropoiesis-stimulating agents; BMI — body mass index

Table III. ThroLy risk score

Patient characteristic	Score
Previous VTE/acute myocardial infarction/stroke	2
Reduced mobility (ECOG 2–4)	1
Obesity (BMI >30 kg/m^2)	2
Extranodal localization	1
Mediastinal involvement	2
Neutrophils <1 ×10^9/L	1
Hb level <10 g/dL	1
ThroLy score points	
0–1 — low risk	
2–3 — intermediate risk	
>3 — high risk	

VTE — venous thromboembolism; ECOG — Eastern Cooperative Oncology Group; BMI — body mass index; Hb — hemoglobin

There are several risks for major bleeding in patients with malignancies: recent major bleeding, abnormal renal function, gastrointestinal manifestation, genitourinary or gynecological localization, thrombocytopenia (<100 ×10^9/L), uncompensated coagulopathy, and metastatic disease in solid tumors [35]. The risk of thrombocytopenia during therapy is relatively high among patients with hematological malignancies [36–38]. Neoplasm localization and concomitant gastrointestinal disease should be evaluated before selecting the appropriate drug. Due to a 36% higher risk of major bleeding on direct oral anticoagulants (DOACs) compared to LMWH, special caution is needed in patients at high risk of bleeding [39–41]. Among cancer patients with an acute diagnosis of VTE and a high risk of bleeding, for patients with luminal gastrointestinal cancers, patients with genitourinary tract cancers, bladder, or nephrostomy tubes, or patients with active gastrointestinal mucosal abnormalities such as duodenal ulcers, gastritis, esophagitis, or colitis, LMWH should be offered. Several anticancer therapies are associated with gastrointestinal toxicities including alkylating agents in high doses (e.g. antimetabolite (e.g. cytarabine, methotrexate), checkpoint inhibitors (e.g. nivolumab) and antimitotic agents (e.g. vinblastin, vincritin) [42].

There are several clinical situations in which anticoagulation may be contraindicated including thrombocytopenia (particularly thrombocytopenia resistant to transfusion), active major bleeding, uncompensated coagulopathy and recent or planned surgery, or invasive procedures (lumbar puncture). If there is active bleeding on therapeutic anticoagulation with contraindication to oral or parental anticoagulation, the placement of an inferior vena cava (IVC) filter may be considered [43].

Drug interactions

In general, LMWH or DOACs can be used as long as there are no contradictions to the selected agent. The choice of anticoagulation should be based both on specific risk factors for patients with malignancy, such as specific risk of bleeding, thrombocytopenia and drug interactions, as well as on factors applying to the general population such as renal/hepatic insufficiency, comorbidities with gastrointestinal disorders or hereditary bleeding diathesis, obesity, *etc.* In general, VKA is not recommended for VTE treatment in cancer patients. LMWH is preferred over VKA because of its superior efficacy and comparable safety based on a meta-analysis [41, 44, 45]. It must be underscored that all hematological malignancies have been underrepresented in clinical trials with DOACs and have constituted 2.5–10.6% of the whole cohort (Table IV) [46].

In patients with renal insufficiency and creatine clearance below 30 mL/min, and where both LMWH is contraindicated and DOACs have not been studied or included in clinical trials, intravenous unfractionated heparin (UFH) may be administered, or small doses of LMWH with monitoring of anti-factor Xa levels. Compared to LMWH, oral anticoagulants, both vitamin K antagonist (VKA) and DOACs, have potential drug interactions with concurrent use of potent P-glipoprotein (minor or none for VKA but major for DOACs) or cytochrome P3A4 inhibitors (major interactions for VKA, apixaban and edoxaban but no metabolic interaction with rivaroxaban).

According to American Society of Clinical Oncology (ASCO) guidelines, both inhibitors or inducers of P-glipoprotein can affect the concentration of all DOACs, while inhibitors or inducers of cytochrome P3A4 may influence rivaroxaban and apixaban to some extent, but without any effects on dabigatran and edoxaban [27]. There is only limited data on specific drug-drug interactions from clinical trials, such as the Hokusai VTE cancer study [47], and therefore the potential benefits and risks between DOACs and

Table IV. Percentage of patients with hematological malignancies included in clinical trials with direct oral anticoagulants (DOACs) for treatment of venous thromboembolism (VTE) in patients with cancer

Study	Hematological malignancies [%]	N	DOAC studied
Hokusai VTE	10.6	1,046	Edoxaban
SELECTED-D	2.5	406	Rivaroxaban
ADAM VTE	9.3	287	Apixaban
CARAVAGGIO	7.4	1,155	Apixaban

cancer therapies should be assessed individually. Doxorubicin, dexamethasone and vinblastine must be mentioned among anti-cancer agents or supportive drugs that may reduce the level of DOACs, including rivaroxaban, apixaban and dabigatran [48]. Combined imatinib with dabigatran, rivaroxaban, and apixaban decreases the level of DOACs [42]. On the other hand, many drugs can increase the level of DOACs and increase the risk of bleeding with nolitinib concomitant use with dabigatran (P-glipoprotein) or rivaroxaban/apixaban by metabolic activity via P-glipoprotein or cytochrome P3A4. Moreover, many anti-mycotic agents, and also cyclosporine, increase plasma factor Xa through P-glycoprotein or CYP3A4 induction and it is suggested to avoid these combinations [42, 48]. Both ibrutinib and venetoclax are P-glycoprotein inhibitors and may increase the level of DOACs.

Recommendations for CAT prevention and treatment

The 2019/2020/2021 updated guidelines from the International Initiative on Thrombosis and Cancer (ITAC), the ASCO, the National Comprehensive Cancer Network (NCCN; version of March 2021), and the American Society of Hematology (ASH) recommend DOACs in the prevention and treatment of CAT [27–31]. Most of the recommendations and suggestions concerning hospitalization, surgery, ambulatory thromboprophylaxis, and CAT treatment are in line with the ASH 2021 guidelines.

VTE prevention in hospitalized patients with cancer

According to the ASH 2021 guidelines, in primary prophylaxis for hospitalized patients with cancer without VTE, the use of thromboprophylaxisis is recommended instead of no thromboprophylaxis. Furthermore, pharmacological thromboprophylaxis is preferred over mechanical thromboprophylaxis. Additionally, in place of a combination of both pharmacological and mechanical thromboprophylaxis, only pharmacological thromboprophylaxis is advised. When using pharmacological thromboprophylaxis for this group of patients, according to the ASH guideline recommendations, LMWH is preferred over unfractionated heparin (UFH), with discontinuation at hospital discharge [28].

Primary prophylaxis for patients with cancer undergoing surgery

The current updated ASH guidelines for patients with cancer without VTE undergoing a surgical procedure with a lower bleeding risk recommend using pharmacological rather than mechanical thromboprophylaxis, except for patients at high bleeding risk, where only mechanical thromboprophylaxis is advised.

A combination of mechanical and pharmacological thromboprophylaxis, rather than mechanical prophylaxis alone, is recommended for patients with cancer without VTE undergoing a surgical procedure and at a high risk of thrombosis, except in patients at high risk of bleeding. Among the available drugs, LMWH or fondaparinux for thromboprophylaxis rather than UFH are recommended in this group of patients. There have been no studies into the use of VKA or DOACs for thromboprophylaxis in patients with cancer undergoing a surgical procedure. Postoperative thromboprophylaxis over preoperative thromboprophylaxis is suggested. In the case of patients with cancer who have undergone a major abdominal/pelvic surgical procedure, pharmacological thromboprophylaxis post-discharge should be continued [28].

Primary prophylaxis in ambulatory patients with cancer receiving systemic therapy

According to the ASH guidelines, no thromboprophylaxis is advised rather than parenteral thromboprophylaxis for ambulatory patients with cancer and a low or intermediate risk of CAT who are receiving systemic therapy. Neither VKA nor DOACs should be offered in the low-risk group, although DOACs (apixaban or rivaroxaban) are advised for the intermediate and high-risk groups. Meanwhile, for ambulatory patients with cancer at a high risk of CAT undergoing systemic therapy, the ASH guidelines recommend parenteral thromboprophylaxis (LMWH) over no thromboprophylaxis.

Patients with multiple myeloma undergoing treatment with thalidomide, lenalidomide or pomalidomide-based regimens can be offered thromboprophylaxis with

low-dose acetylsalicylic acid (ASA) or fixed low-dose VKA or LMWH [28].

Treatment of CAT

Initial treatment (first week) for patients with active cancer and VTE

According to the ASH guidelines, initial treatment of CAT (first week) should comprise DOAC (apixaban or rivaroxaban) or LMWH (over UFH) for patients with active cancer and VTE.

Short-term treatment for patients with active cancer (initial 3–6 months)

According to the ASH guidelines, DOACs (apixaban, edoxaban, or rivaroxaban) over LMWH are suggested for the short-term treatment of VTE (3–6 months) for patients with active cancer. In the current ASH guidelines, incidental (unsuspected) pulmonary embolism (PE) and/or subsegmental PE in patients with cancer should be treated with short-term anticoagulation, rather than just being observed. For patients with cancer and visceral/splanchnic vein thrombosis, there is a choice between treatment with short-term anticoagulation or observation.

Long-term treatment (>6 months) for patients with active cancer and VTE

The ASH guidelines recommend the implementation of long-term anticoagulation for secondary prophylaxis (>6 months) rather than only short-term treatment (3–6 months) in patients with CAT. Meanwhile, the guidelines recommend the continuation of indefinite anticoagulation rather than complete cessation in patients with active cancer and CAT after completion of a definitive period of anticoagulation. Among anticoagulation agents, DOACs are preferred over LMWH in this group of patients, continuing anticoagulation >6 months [28].

Patients with cancer with central venous catheter

The updated ASH guidelines for 2021 do not recommend the administration of parenteral or oral thromboprophylaxis for patients with cancer and a central venous catheter (CVC). They recommend not removing the CVC in patients with cancer presenting CVC-related VTE receiving anticoagulants, and instead leaving the CVC in place [28].

Conclusion

The available VTE risk-assessment models are not useful in predicting VTE risk in patients with hematological neoplasms. Further research on primary prophylaxis is required, especially in patients with hematological malignancies. The ASH guidelines suggest that mortality, pulmonary embolism, deep venous thrombosis, and major bleeding including risks of thrombocytopenia, are major factors when considering thromboprophylaxis and CAT treatment in cancer patients including hematological malignancies.

Author's contributions

JR-M — sole author.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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