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PALLIATIVE MEDICINE (A JATOI, SECTION EDITOR)

Prophylactic Anticoagulation in Patients with Cancer: When and How?

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Abstract

Purpose of Review Cancer-associated thrombosis is a leading cause of death among patients with cancer. Historically, thromboprophylaxis efforts have focused on the highest risk patients with cancer, including post-operative patients and hospitalized patients. This review covers not only thromboprophylaxis for these groups but also emerging data supporting prophylaxis in ambulatory medical oncology patients.

Recent Findings Several leading guidelines, backed by clinical trial data, now support the use of direct oral anticoagulants for select high-risk outpatients for primary thromboprophylaxis. However, uptake of these findings remains low. Pharmacologic venous thromboembolism prophylaxis strategies continue to improve. However, it remains challenging to balance competing risks of bleeding and thrombosis.

Summary The morbidity and mortality associated with cancer associated thrombosis may be preventable. Understanding advancements in risk prediction, anticoagulant options, and implementation of existing data, is critical to provide optimal patient care.

Keywords Venous thromboembolism · Cancer · Anticoagulants · Preventative care · Factor Xa inhibitors · Low molecular weight heparin

Introduction

Venous thromboembolism (VTE) is a major, potentially preventable cause of morbidity and mortality affecting 1–2 individuals of every 1000 per year; this equates to approximately 500,000 VTE annually in the USA [1]. Complications include sudden death in up 25% of patients and post-thrombotic syndrome in 20–50%, and up to 5% of patients develop chronic thromboembolic pulmonary hypertension [1]. The burden of VTE is especially high among patients with cancer, who represent 15–20% of all patients with thrombosis [2, 3••]. Approximately 4–20% of patients with cancer have a course complicated by VTE, but incidence varies depending on patient, malignancy, and treatment-related factors [4]. Cancer-associated thrombosis (CAT) can delay cancer-directed therapy, increase healthcare costs, and is the leading non-cancer cause of death among these patients [5].

Oncology providers are aware of the risks of VTE among patients with cancer [6], but prophylaxis rates are suboptimal for surgical, hospitalized, and ambulatory medical oncology patients [6–8, 9••, 10–18]. While guidelines on VTE prophylaxis [3••, 19••, 20••, 21••] are available, they are not always followed in clinical practice. The reasons why clinical practice diverges from guidelines is not well established. It could be due to limitations in the data supporting guideline recommendations, providers not being aware of recommendations or confident in managing prophylactic anticoagulants, drug access issues, time constraints, and several other factors. Applying these guidelines to individual patients and balancing competing risks of thrombosis versus bleeding can be challenging, as patients with malignancy have a 2–3-fold higher risk of major hemorrhage on anticoagulation [22]. It requires not only a foundational understanding of the data behind the guidelines but also strategies for successful implementation.

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This review will highlight the latest advances in the field of CAT prophylaxis and help readers guide their patients in determining an appropriate thromboprophylaxis strategy. Specifically, the review will help readers determine when pharmacologic thromboprophylaxis should be considered and how to select an appropriate anticoagulant. Continued advances in the field combined with efforts to improve implementation will ultimately translate to improved patient outcomes and a lower incidence of CAT.

When to Consider Prophylaxis

Guideline recommendations pertaining to prophylaxis are regularly updated, and therefore, it is best to reference these frequently to ensure all appropriate factors are considered when making prophylaxis decisions. Organizations including the National Comprehensive Cancer Network (NCCN) [19••], the American Society of Hematology (ASH) [3••], the International Society of Thrombosis and Hemostasis (ISTH) [21••], and the American Society of Clinical Oncology (ASCO) [20••] have developed guidelines for VTE prophylaxis in patients with cancer [23]. Many of these recommendations are conditional, based on low or moderate certainty in the evidence. Multiple VTE risk score models exist for hospitalized patients; however, none of them have been prospectively validated in patients with cancer [24–26]. The Khorana risk score was developed to predict patients most at risk for VTE and is validated by large studies including a variety of cancer types. However, when evaluated by type of cancer, it may be less able to identify patients who will develop VTE [27, 28]. In addition to thrombotic risk, additional considerations for thromboprophylaxis decisions include bleeding risk, thrombocytopenia secondary to disease or treatment, kidney and liver function, and drug interactions. Many institutions maintain their own clinical practice guidelines that should also be considered with thromboprophylaxis decisions.

Risk assessment and consideration of prophylaxis are generally considered for patients with cancer who are hospitalized, undergo surgery, and/or high-risk outpatients. We will review a step-wise approach for determining when and how to institute prophylaxis for these three general groups (Table 1). There are unique considerations for patients with myeloproliferative neoplasms and multiple myeloma that are not covered here.

Contraindications to Prophylaxis

One of the first steps in developing a VTE prophylaxis plan is to assess for contraindications to pharmacologic prophylaxis. Prophylactic anticoagulation is generally contraindicated in patients who are actively bleeding or at high risk for hemorrhage, including those with significant thrombocytopenia (generally platelets < 25,000–50,000/μL, but this threshold is not well established and therefore requires clinical judgement), patients with an underlying hemorrhagic coagulopathy, including disseminated intravascular coagulation, or known bleeding disorders such as hemophilia or von Willebrand disease [29]. Indwelling neuraxial catheters, neuraxial anesthesia, lumbar punctures, interventional spine, and pain procedures can also be contraindications to prophylactic anticoagulation [29]; institutional, anesthesia, and the latest CAT-specific guidelines should be referenced in these situations that may also necessitate multidisciplinary discussion. Even if not contraindicated, bleeding risk factors should be considered and, when possible, optimized for all patients [30]. When the bleeding risk is unacceptably high or pharmacologic anticoagulation is contraindicated, mechanical methods of prophylaxis can be considered [29].

There are important contraindications to specific anticoagulants. Low molecular weight heparin (LMWH) is excreted in the urine and therefore should be dose-reduced or avoided in patients with severe renal dysfunction (CrCl < 30 mL/min). Both LMWH and unfractionated heparin are contraindicated for patients with a history of heparin induced thrombocytopenia (HIT). Fondaparinux should be used with caution for patients with CrCl ≤ 30–49mL/min, advanced age, or low weight; it is contraindicated for those with CrCl < 30 mL/min. Patients with a history of stomach and/or proximal small bowel resections may have suboptimal absorption of all direct oral anticoagulants (DOACs), and those with resection of a significant amount of colon may also have difficulty absorbing apixaban. Trials on the treatment, rather than prophylaxis of CAT, HOKUSAI-VTE, and SELECT-D, demonstrated an increased risk of gastrointestinal bleeding with edoxaban and rivaroxaban, respectively, compared to dalteparin [31, 32]. An increased bleeding risk has not been clearly shown with apixaban in CAT; however, fewer patients were included with upper gastrointestinal (GI) malignancies [33, 34]. There are a number of hypotheses to explain the increased risk of GI bleeding with DOACs in patients with cancer. These includes tumor-driven angiogenesis resulting in an increased intestinal blood supply, damage to the GI mucosa due to chemotherapy, increased exposure due to P-glycoprotein efflux, and potentially a direct topical anticoagulant effect for rivaroxaban as it is the only DOAC absorbed in the stomach [35].

The DOACs are generally avoided in the setting of moderate to severe renal impairment (CrCl < 30 mL/min), active liver disease, unavoidable drug interactions and potentially genitourinary or gastrointestinal tract lesions, pathology, or instrumentation [29, 36].

Table 1 Strategies for VTE prophylaxis among patients with cancer

Context	Potential prophylaxis strategies	Notes
Hospitalized patients		
Contraindication to pharmacologic prophylaxis, contraindication or inability to administer mechanical prophylaxis	Early ambulation when possible, patient education, regular reassessment	--This situation is rare --Limited data and guidelines to guide management
Contraindication to pharmacologic prophylaxis, without contraindication to mechanical prophylaxis	Mechanical prophylaxis (sequential compression devices generally preferred over graduated compression stockings)	--Data to support mechanical methods largely extrapolated from surgical or stroke patients
No contraindications to pharmacologic prophylaxis	Dalteparin, enoxaparin, fondaparinux, subcutaneous unfractionated heparin	--Consult institutional guidelines --Dalteparin and fondaparinux should be avoided if CrCl < 30 mL/min, enoxaparin may require dose reduction --Fondaparinux should be avoided in patients < 50 kg and caution is needed given the long half-life --Dose adjustments may be needed for obesity --Heparin and related drugs must be avoided for patients with a history of HIT
No contraindications to pharmacologic prophylaxis, CrCl < 30 mL/min	Subcutaneous unfractionated heparin	--Contraindicated with a history of HIT
No contraindications to pharmacologic prophylaxis, desires daily dosing	LMWH, fondaparinux	
Ambulatory Medical Oncology outpatients with active cancer[a]		
Khorana score < 2	Patient education	--Pharmacologic prophylaxis is not routinely indicated for low-risk patients --It is reasonable to educate patients on the signs/symptoms of VTE and conservative risk reduction strategies
Khorana score ≥ 2, acceptable bleeding risk, no drug interactions, receiving/starting systemic therapy	Apixaban, rivaroxaban, dalteparin, enoxaparin	--Avoid if CrCl < 30 mL/min or platelets under 50,000 --Avoid apixaban and dalteparin if weight < 40 kg --LMWH has largely been studied in advanced unresectable or metastatic pancreatic cancer --DOACs may not be well absorbed in patients with altered gastrointestinal anatomy; patients with gastric and gastroesophageal tumors are likely at increased risk of bleeding with DOACs
Khorana score ≥ 2, bleeding risk factors OR prefers not to be on prophylaxis OR unavoidable drug interactions OR significant liver or kidney disease	Patient education	--The anticipated benefits of prophylaxis may not outweigh the risks with patients at increased risk for bleeding --Drug interactions, bleeding risk, organ dysfunction, or other factors may preclude pharmacologic VTE prophylaxis

CrCl creatinine clearance, *DOACs* direct oral anticoagulants, *kg* kilograms, *VTE* venous thromboembolism

[a]Excludes multiple myeloma, acute leukemia, myeloproliferative neoplasms, primary or metastatic brain tumors. See text for details

Inpatient Prophylaxis

All hospitalized medical and surgical patients with a diagnosis or strong clinical suspicion for malignancy are likely at risk for developing VTE and should be considered for VTE prophylaxis. The NCCN guidelines recommend all eligible patients hospitalized with cancer receive VTE prophylaxis, excluding patients with basal cell or squamous cell skin cancer or those who no longer have an active cancer diagnosis [29]. ASCO guidelines recommend all hospitalized patients with active malignancy or acute illness be offered prophylaxis unless there is a bleeding risk or other contraindication. However, they advise that patients admitted for minor procedures or chemotherapy administration should not be routinely offered pharmacologic thromboprophylaxis [20••]. The ASH guidelines also suggest thromboprophylaxis in hospitalized patients with malignancy, recommending pharmacologic prophylaxis over mechanical prophylaxis, unless contraindicated [3••]. Data to support guideline recommendations are largely extrapolated from studies in hospitalized medical patients, among whom only 5–15% had a cancer diagnosis and baseline characteristics for these patients are unknown. Thus, these studies may not account for factors potentially relevant to this population, including disease burden and treatments. As with all anticoagulation decisions, providers should participate in shared decision making with their patients. Patients should be educated on signs, symptoms, and risk factors for VTE along with the risks and benefits of prophylaxis.

Among patients with a contraindication to prophylactic anticoagulation, intermittent pneumatic compression (IPC) should be implemented when appropriate. Development of deep vein thrombosis was significantly reduced with IPC compared to graduated compression stockings (GPC) with a lower risk of skin complications [29, 37].

For hospitalized medical oncology patients, recommended anticoagulants include dalteparin, enoxaparin, fondaparinux, and unfractionated heparin (Table 2). If a patient is receiving prophylactic dosing apixaban or rivaroxaban as an outpatient, these medications may be continued, but generally should not be initiated in the hospital [29]. Of note, continuing these medications inpatient may not be appropriate or advised given potential organ dysfunction, drug interactions, and/or patient instability. Table 2 outlines anticoagulants commonly used for hospitalized surgical patients.

Prophylaxis upon Discharge

For surgical oncology patients, anticoagulant prophylaxis may be considered from the pre-operative period through beyond hospital discharge [29]. In practice, mechanical

Table 2 Characteristics of anticoagulants commonly used in the prophylaxis of CAT

	Direct oral anticoagulants		LMWH (enoxaparin, dalteparin)	Unfractionated heparin	Fondaparinux
	Apixaban	Rivaroxaban			
Mechanism	Factor Xa inhibitor	Factor Xa inhibitor	Inhibition (through antithrombin III) of factor Xa and IIa (Xa/IIa is 3–4:1)	Inhibition (through antithrombin III) of factor Xa and IIa (Xa/IIa is 1:1)	Inhibition (through antithrombin III) of factor Xa
Renal clearance	27%	66% (30% as inactive metabolites)	8–40% (10% unchanged)	Minimal, dose dependent[b]	77%
CYP3A4 substrate	Yes	Yes	No	No	No
Impacted by P-glycoprotein transporter system	Yes	Yes	No	No	No
Bioavailability	50%	80–100%[a]	80–100% (subq)	30–70% (subq), potentially reduced in obesity, dose dependent	100% (subq)
Half-life	8–15 h	5–9 h	3–7 h	1.5 h (variable)	17–21 h
Dosing frequency	Twice daily	Daily	Twice daily or daily	Twice daily or three times daily	Daily
Administration	Oral, without regard to food	Oral, without regard to food[a]	Subcutaneous	Subcutaneous	Subcutaneous
Monitoring	Renal and hepatic function, platelets	Renal and hepatic function, platelets	Renal function, platelets	Platelets	Renal function, platelets
Storage	Room temperature	Room temperature	Room temperature	Room temperature	Room temperature

[a]Comment applies to prophylactic dose of rivaroxaban (10 mg). Rivaroxaban doses ≥ 15 mg must be taken with food to improve bioavailability

[b]Eliminated primarily by the reticuloendothelial system; at very high doses with saturation of reticuloendothelial clearance, renal clearance may increase, although no dose adjustments necessary

methods are often added to pharmacologic prophylaxis in particularly high-risk patients, though data have not clearly shown this practice to be beneficial [38]. Upon discharge from the hospital, surgical oncology patients with a low bleeding risk should generally receive pharmacologic VTE prophylaxis for up to 4 weeks postoperatively for high-risk patients undergoing intrabdominal or pelvic surgeries. High-risk patients include those with a prior history of VTE, age over 60, obesity, being under anesthesia for over 2 h, resection of gastrointestinal malignancies, four or more days of required bedrest, and advanced-stage disease. Surgical patients with malignancy at high risk for bleeding should receive mechanical prophylaxis when appropriate [20••, 29], which is typically discontinued upon hospital discharge.

In largely non-oncology populations, there have been several notable recent studies of extended thromboprophylaxis for up to 45 days after hospitalization for medical patients [39]. This has included the ADOPT trial of apixaban, the MAGELLAN trial of rivaroxaban, the APEX trial of betrixaban, and the MARINER trial that also studied rivaroxaban. Based on the results of the MAGELLAN trial, the Food and Drug Administration approved rivaroxaban for thromboprophylaxis for select acutely ill medical patients at risk for VTE but not at high risk of bleeding. However, as above, active cancer is a risk factor for bleeding. Risk assessment models (RAMs) including the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) RAM have been utilized to improve VTE risk prediction [39]. While these data are informative, these prophylaxis strategies and RAMs have not been validated in management studies for hospitalized medical or surgical patients with cancer and therefore they are not routinely employed for this population [29].

Prophylaxis for Ambulatory Medical Oncology Outpatients

Some of the latest advancements in CAT prophylaxis are for high-risk oncology outpatients. For more than a decade, trials have shown a potential benefit for the use of thromboprophylaxis for ambulatory cancer patients. For example, the PROTECHT trial published in 2010 showed a lower incidence of CAT with nadoparin compared to placebo (2% versus 3.9%) among 1150 patients receiving chemotherapy for metastatic or locally advanced solid tumor malignancy with no significant impact on major bleeding [40]. Similarly, the randomized SAVE-ONCO trial published in 2012 found that the ultra-LMWH semuloparin was associated with a significantly lower incidence of CAT compared to placebo (12.% versus 3.4%) among 3212 patients with metastatic or locally advanced solid tumors receiving chemotherapy [41]. Despite apparent efficacy [42], uptake of prophylaxis was low, potentially due to the estimated number needed to treat (NNT) being over 40–50 in unselected patients, an increased risk of bleeding, and the burden of adding injections [21••].

CAT risk assessment models have been utilized to help identify a population of cancer patients at highest risk for thrombosis. The Khorana risk stratification score was originally introduced in 2008 and is currently endorsed by CAT guidelines to assist in risk stratification [3••, 19••, 20••, 21••], and guide decisions for thromboprophylaxis [19••, 20••]. This score contains five predictive variables: primary tumor site, platelet count of 350×10^9/L or more, hemoglobin concentration of 100 g/L or lower or use of erythropoiesis-stimulating agents, leukocyte count of 11×10^9/L or higher, and a body mass index (BMI) of 35 kg/m^2 or higher [43]. The Khorana score has been well validated, and extensively studied [44, 45]. However, it may have some limitations for risk prediction within specific cancer types [27, 28] and given that it does not account for all potential VTE risk factors.

Risk-adapted prophylaxis was utilized by the CASSINI [46•] and AVERT [47•] clinical trials that studied rivaroxaban and apixaban, respectively. The phase 3 CASSINI trial [46•], compared rivaroxaban 10 mg once daily ($n = 420$) to placebo ($n = 421$) for thromboprophylaxis in patients with solid tumors or lymphoma. Rivaroxaban failed to meet the primary endpoint of lower incidence of VTE or death due to VTE during the 180-day trial period compared to placebo (6% vs 8%, $p = 0.10$). However, the incidence of CAT was lower among patients in the rivaroxaban (2.6%) group than in the placebo (6.4%) group in the prespecified intervention period analysis (hazard ratio (HR), 0.40; 95% CI, 0.20 to 0.80) with low incidence of major bleeding (2.0% in the rivaroxaban group and 1.0% in the placebo group (HR, 1.96; 95% CI, 0.59 to 6.49)) [46•]. The lack of significance during the 180-day study period is potentially due to the high premature discontinuation rate (50.2% rivaroxaban, 43.7% placebo). In a post hoc analysis of the CASSINI trial, among patients with gastric/gastroesophageal junction tumors, the incidence of major bleeding was 4.6% with rivaroxaban versus 1.2% with placebo and the site of bleeding was more frequently in the GI tract (3.4% vs 0%) [48]. In the AVERT trial, patients with solid tumors, lymphoma, or myeloma were randomized to apixaban 2.5 mg twice daily ($n = 291$) or placebo ($n = 283$). The incidence of CAT was significantly lower in the apixaban (4.2%) group compared to the placebo (10.2%) group (HR, 0.41; 95% CI, 0.26 to 0.65; $p < 0.001$). Major bleeding occurred in 3.5% of patients in the apixaban group and in 1.8% in the placebo group (HR, 2.00; 95% CI, 1.01 to 3.95), and this difference was mainly among patients with GI and gynecologic malignancies [47•]. This increase in bleeding with apixaban was not seen in the apixaban cancer-associated VTE treatment studies, and may

be due to the high rate of concomitant antiplatelet use in this study (23%). Discordance between CASSINI and AVERT may be attributed to differences in baseline characteristics and study design. In CASSINI, more patients with solid tumors had metastatic disease (54.5% vs 33.8%), fewer patients had prior VTE (1.7% vs 3%), and fewer patients had hematologic malignancies (7% vs 27.9%). In CASSINI, screening ultrasonography was performed four times throughout the study period, whereas it was not routine in AVERT, which may explain the higher rate of asymptomatic/incidental events in the CASSINI trial (27/62 events (43.5%) vs 9/40 events (22.5%)). Overall, the CASSINI and AVERT trials provide evidence of the efficacy and safety of DOACs for CAT prevention, although caution should be used for patients at a high risk of bleeding, particularly those with GI or genitourinary malignancies. While the NNT remained relatively high (NNT = 17–35) to prevent one episode of VTE in the intention to treat analysis [49], among patients on treatment, the NNT was lower at 16–26 [21••], which is similar to the NNT for VTE prophylaxis used in other settings. This likely accounts for the inclusion of the option of DOACs for CAT prophylaxis among outpatients by major guidelines on this topic [3••, 19••, 20••, 21••].

Identifying Candidates for Outpatient Thromboprophylaxis

Active cancer is generally defined by the ISTH as cancer diagnosed within the previous 6 months; recurrent, regionally advanced or metastatic cancer; cancer for which treatment had been administered within 6 months; or hematological cancer that is not in complete remission. However, variable definitions have been used in clinical trials [50].

Guidelines suggest that ambulatory patients with active cancer (excluding multiple myeloma, acute leukemia, myeloproliferative neoplasms, and patients with primary/metastatic brain tumors) receiving or starting systemic cancer therapy be risk stratified, with consideration of anticoagulant prophylaxis for up to 6 months or longer for patients with a Khorana score ≥ 2 [29]. Systemic cancer therapy included hormonal treatment in the AVERT trial, but these patients were excluded from the CASSINI study. While factor Xa inhibitors are most commonly considered for prophylaxis, LMWH has been considered for select high-risk patients who are ineligible for DOACs [21••, 29]. Data to support the use of LMWH are largely from studies of patients with advanced unresectable or metastatic pancreatic cancer [29].

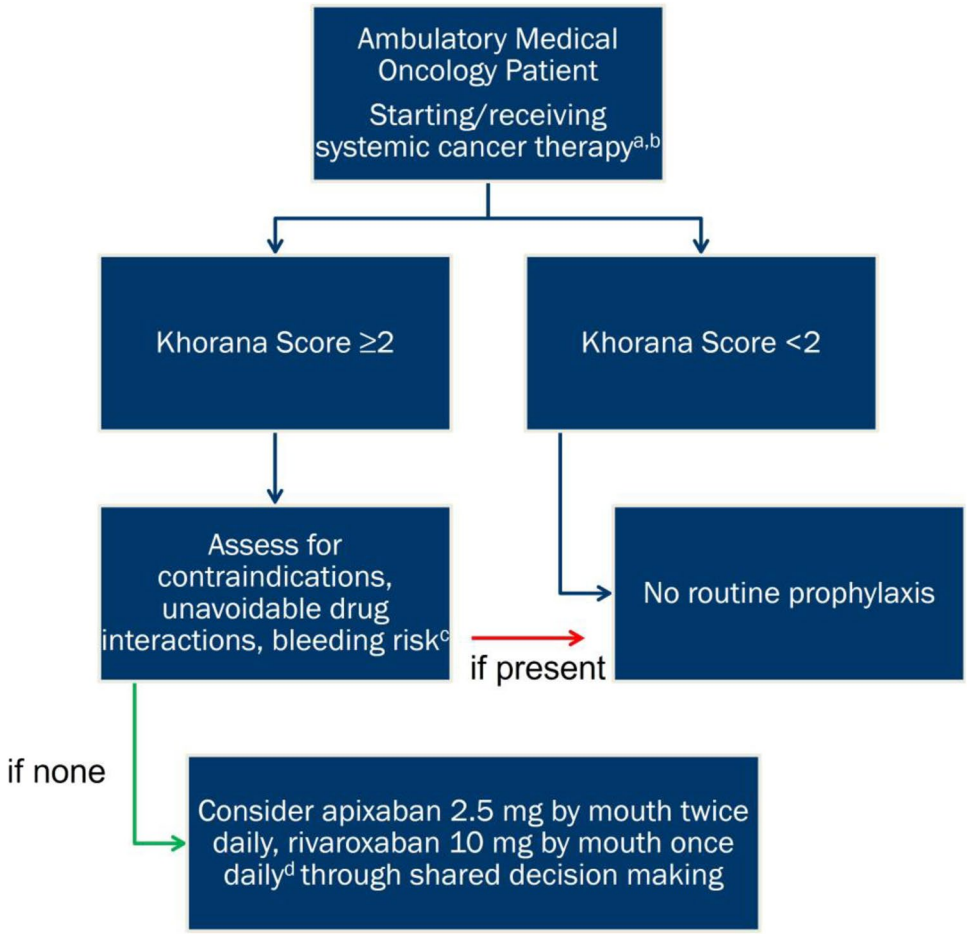

Fig. 1 Flow chart on selecting ambulatory medical oncology patients for pharmacologic venous thromboembolism prophylaxis. Adapted from guideline recommendations [29 and with permission from the Michigan Anticoagulation Quality Improvement Initiative (anticoagulationtoolkit.org). A This flow chart applies to patients with active cancer excluding patients with multiple myeloma, myeloproliferative neoplasms, primary or metastatic brain tumors, planned stem cell transplant, hospitalized, or post-operative patients. B Patients receiving hormonal therapy were excluded from the AVERT trial but not the CASSINI trial. C See text for discussion of some contraindications to prophylactic anticoagulation. It is recommended that providers review the latest guidelines for cancer associated thrombosis and their institutional guidelines, review management with a pharmacist, and assess patient specific bleeding risk

Implementation Considerations

Practically, when caring for outpatients with cancer who are receiving or starting systemic therapy, it is reasonable to start by calculating the Khorana score for patients without contraindications to anticoagulation. For patients with a score ≥ 2, we assess their candidacy for prophylaxis by evaluating their bleeding risk and for any drug interactions with the DOACs (Fig. 1). For patients at high risk for thrombosis, with no significant drug interactions, and an acceptable bleeding risk, a discussion on the risks and benefits of thromboprophylaxis with the DOACs should ensue (Table 1). Patients electing to start pharmacoprophylaxis are subsequently followed to assess for drug tolerance, adherence, organ dysfunction, significant thrombocytopenia, or otherwise that may influence the ongoing use of anticoagulation. Guidelines suggest a duration of therapy of up to 6 months or longer, as long as thrombotic risk persists.

Instituting thromboprophylaxis in this context does add additional effort for patients that may already have extensive care needs with their cancer, the related therapy, and supportive care. However, studies show that it is feasible to improve CAT prophylaxis rates as demonstrated by Holmes et al. [9••]. They referred 141 out of 151 high-risk medical oncology outpatients to hematology and ultimately instituted prophylaxis for 93.8% of patients [9••]. While a variety of strategies have been shown to successfully improve thromboprophylaxis for hospitalized and surgical patients [51•], prophylaxis remains underutilized or misapplied [52•]. While provider knowledge of guidelines may be one barrier [7], there remains a need for better understanding of barriers and facilitators to optimizing VTE prophylaxis, especially among outpatients. Further research should focus on determining the optimal strategy to implement guidelines in clinical practice and facilitate shared decision making with patients. Hopefully ongoing studies, including investigations of the use of factor XI inhibitors, will lead to improvements in the safety and effectiveness of thromboprophylaxis for CAT.

Conclusion

While CAT continues to be a major source of morbidity and mortality among patients with cancer, appropriate thromboprophylaxis may mitigate this risk. VTE risk reduction strategies remain paramount for patients with cancer, especially those who are hospitalized or in the postoperative setting. Improvements in risk prediction and pharmacotherapy have expanded the reach of prophylaxis now to the outpatient setting. There remains a need to improve the implementation of existing data to optimize patient outcomes.

Declarations

Conflict of Interest Dr. Schaefer reports grant support from American Society of Hematology. The remaining of authors disclosed no potential conflicts of interest.

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•• Of major importance

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