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Choosing wisely, Anticoagulants in venous thromboembolism treatment and prophylaxis in adult cancer patients

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Abstract

Venous thromboembolism is common in cancer patients, and guidelines to prevent and treat cancer-associated VTE are changing with new evidence. DOACs are increasingly becoming popular due to their efficacy, reasonable safety, and convenience to use, replacing the previous standard of care LMWH. Although more clinicians are using DOAC in the treatment and prevention of VTE many international society guidelines are still reluctant to accept DOAC as a first-line agent. This review article will summarize old and recent studies to compare the safety and efficacy of different anticoagulation options.

Keywords: Anticoagulation, Cancer-Associated Thromboembolism (CAT), Direct oral anticoagulants (DOACs), Low Molecular Weight Heparin (LMWH), Warfarin, Khorana score.

Introduction

Venous thromboembolism is the second major cause of death in the cancer patient population after cancer itself. Clinically apparent VTE occurs in as many as 10 percent **[1]** of patients with cancer and even higher in some cancers, e.g. 30-40 % of patients with pancreatic body and tail cancer.**[2]**

The treatment and prevention of VTE in cancer patients have been complex due to the high risk of recurrence, the need for prolonged use of anticoagulation, and a higher risk of bleeding in these patients. Compared with the general population, cancer patients have a 4 to 7 fold increased risk of VTE and a 2-fold increased risk of major bleeding on anticoagulation.**[3]**

Thrombotic events can present in different forms, such as superficial thrombophlebitis, deep vein thrombosis, sterile (marantic) endocarditis, DIC, TTP, or even arterial thrombosis.

Multiple treatment options are available, including a daily or twice-daily dose of LMWH, DOACs including Apixaban, Rivaroxaban, Edoxaban, direct thrombin inhibitors, e.g., Dabigatran and Fondaparinux and Vitamin K inhibitor, e.g., warfarin.

Discussion

Thrombosis pathogenesis in cancer patients

Several mechanisms have been proposed**[4]** to explain the strong association of thrombosis in cancer patients but remain incompletely understood.

Cancer cells secrete high levels of Tissue Factor or TF-positive microparticles. TF is a transmembrane protein, present in normal cells too, but usually, the degree of differentiation of cancers cells is inversely related to TF expression on the cell membrane. These TF's then make a complex with FVIII and activate FIX and FX, starting a coagulation cascade. Pancreatic, colorectal, clear cell ovarian cancer and Acute Promyelocytic Leukemia (APL) are examples of tumors secreting TF.

Some other cancer-related procoagulants like calcium-dependent cysteine protease directly activate FX bypassing other factors in the coagulation cascade. Tumor cells also produce cytokines TNF and IL-1, activating endothelial cells, causing a procoagulant state. Other mechanisms may be platelet activation by ADP secretion, increased thrombin secretion, P-Selectin secretions by tumor cells (activates

platelets). Thrombocytosis, leukocytosis such as in blast crisis, increase the viscosity of blood and increase the risk of thrombosis,

Large tumors can directly compress over vessels, or some can grow within vessels like RCC can infiltrate IVC causing obstruction and increasing riks of DVT.

Some chemotherapy agents like thalidomide, lenalidomide, pomalidomide, tamoxifen, bevacizumab, and high-risk surgeries, especially abdominal and pelvic, increase the risk of VTE.

Primary prophylaxis

Although there is an increased risk of VTE in cancer patients, many studies have shown that risk is even higher during the first year of diagnosis and at the start of new chemotherapy. The presence of metastatic disease at the time of diagnosis is a major predictor of VTE.

Multiple scoring systems have been developed to stratify the risk of VTE in ambulatory cancer patients. Khorana score is the most used score and has been validated in many studies.**[5]** It was developed in 2008 to stratify cancer patients' risk, receiving chemotherapy.

Khorana score

Patient's characteristics	**Risk Score**
very high-risk cancer (stomach, pancreas)	2
high-risk cancer (lung, lymphoma, gynecological, bladder, or testicular)	1
Pre chemotherapy platelet count ≥ 350 x 10^9 /L	1
Pre chemotherapy hemoglobin level < 10 g/dl or use of RBC growth factors e.g, erythropoietin	1
Pre chemotherapy WBC count ≥ 11 x 10^9 /L	1
Body Mass Index ≥ 35 kg/m^2	1

Score 1-2: Intermediate Risk: 1.8 - 2.0 % risk of VTE at 2.5 months. Score ≥ 3: High Risk: 6.7 - 7.1 % risk of VTE at 2.5 months.

Several studies have been done in the past and recent years to evaluate the benefits of primary prophylaxis.

PROTECHT (2009) and SAVE-ONCO (2012)**[6,7]** trials, both of which evaluated the benefits of primary VTE prophylaxis in the cancer population, showed that prophylaxis with LMWH reduces the incidence of thromboembolic events in cancer patients receiving chemotherapy without any significant increase in major bleeding risk. Although these trials showed the benefits, the absolute risk reduction was not significant, with no mortality difference.

AVERT (2018) trial **[8]** showed the use of low dose apixaban in intermediate to high risk (Khorana score ≥ 2) cancer patients reduces the risk of venous thromboembolism but also increased the risk of major bleeding episodes.

CASSINI (2019) a recent trial **[9]** used low dose rivaroxaban in the same population with (Khorana score ≥ 2, didn't show a statistically significant reduction in the incidence of VTE or death at 180 days, also demonstrated a marginally increased risk of major bleeding events with rivaroxaban.

Based on the above studies, the guidelines were updated by both ASCO and NCCN in 2019.

Current VTE Prophylaxis guidelines [10,11]
ASCO urges to intensify the use of VTE prophylaxis and recommends considering VTE prophylaxis in cancer patients with Khorana score ≥ 2 and the patients with multiple myelomagetting thalidomide/ lenalidomide based therapy and/or dexamethasone, should be offered primary prophylaxis. Preferred agents for prophylaxis are LMWH, Apixaban, or Rivaroxaban
NCCN doesn't recommend routine use of prophylaxis except in very high-risk multiple myeloma patients. When selecting an agent for prophylaxis no direct comparative studies ofLMWH with DOACs or among Direct oral anticoagulants are available. No particular guidelines on the duration of anticoagulation are available.
ITAC does not recommend routine use of primary VTE prophylaxis in ambulatory cancer patients receiving systemic anticancer therapy unless moderate to high risk for VTE (Khoranascore ≥ 2), locally advanced or metastatic pancreatic cancer treated with systemic anticancer, or patients getting treatment with immunomodulatory drugs combined with steroids.

Recommends prophylaxis in cancer patients with reduced mobility.
Acute settings: Primary VTE prophylaxis is recommended in all cancer patients (Unlesscontraindicated) in acute illness like during hospitalization and perioperatively in major surgery, just like in the general population. Combining mechanical with pharmacological prophylaxis increases efficacy and is recommended but, Mechanical prophylaxis is not recommended alone.

While there is an increased risk of VTE and risk of bleeding in cancer patients, it should be kept in mind that most of the patients with cancer do not develop VTE.

Treatment and Secondary Prophylaxis

Treatment of VTE in cancer patients is more complicated due to the increased risk of recurrence and bleeding risk than in the general population. LMWH has been shown to decrease the risk of recurrent VTE with a low risk of bleeding in cancer patients as compared to long-term warfarin in multiple trials (CATH, CLOT, CATHENOX), clearly establishing the superiority of LMWH. Therefore, the standard of care for the treatment of CAT has been LMWH for the last 15 years. Recent studies show that DOACS has similar efficacy without significantly increased risk of major bleeding as compared to LMWH.

The ADAM trial (2017) **[12]** was a randomized, open-label study to compare apixaban efficacy/ safety with dalteparin in CAT treatment. Results showed that apixaban was associated with low VTE recurrence (HR 0.099, 95 % CI, 0.013-0.780, *P* = .028) and low major bleeding risk as compared to LMWH (0 % vs. 1.4 %).

SELECT-D **[13]** a pilot study (2018) compared LMWH and Rivaroxaban for treatment of cancer-associated VTE, results showed a reduced risk of recurrent VTE with rivaroxaban compared to LMWH (HR 0.43; 95 % CI 0.19-0.99), No statistically significant increased risk of major bleeding (HR 1.83; 95 % CI 0.68-4.96) but with increased risk of non-major bleeding (HR 3.76; 95 % CI 1.63-8.69)

HOKUSAI VTE **[14]** trial (2018) provided a comparison of LMWH with Edoxaban (after 5 days of LMWH). The results demonstrated that Edoxaban reduces the risk of recurrent VTE (Noninferior to dalteparin; HR 0.97; 95 % CI 0.70-1.36; P=0.006 for noninferiority) but increases the risk of major bleeding (HR 1.77; 95 % CI 1.03-3.04; P=0.04). Patients with GI malignancies were noted to have more bleeding with Edoxaban than dalteparin.

CARAVAGGIO **[15]** trial (2020), a non-inferiority clinical trial showed that oral apixaban was non-inferior to dalteparin in preventing recurrent VTE (HR 0.63; 95 % CI 0.37 - 1.07; p < 0.001 for non-inferiority) and also didn't show any increased risk of major bleeding compare to dalteparin (HR 0.82; 95 % CI 0.40 - 1.69).

A recent meta-analysis **[16]** of 14 studies also showed that DOAC's are effective to prevent VTE recurrence in patients with CAT but are associated with an increased risk of bleeding compared to LMWH.**[15]**

CANVAS **[17]** is a randomized trial study currently going on, aiming to compare DOACs vs. LMWH vs. LMWH followed by warfarin directly. We believe that the results will give us a broad perspective of the efficacy and safety of all main 3 treatment regimens.

Current guidelines for CAT treatment options [10,11,18]
ACCP does not have updated guidelines based on the recent trials of DOACs. The latest guidelines from 2016 still recommend treatment of cancer-associated VTE with LMWH overVKA or any other DOACs. (Although DOACs are recommended over LMWH or warfarin forVTE treatment in non-cancer population)
American Society of Clinical Oncology (ASCO) updated guidelines in 2019 and added Rivaroxaban and Edoxaban (only after 5 -10 days of parenteral anticoagulation) to treat CATalong with LMWH. UFH only in case of severe renal impairment (GFR < 30L/min). Apixaban was only recommended for primary prophylaxis.
The National Comprehensive Cancer Network (NCCN) updated guidelines in 2018 recommend LMWH as monotherapy or LMWH followed by Edoxaban as category 1 options to treat cancer-associated VTE. Other monotherapies and combinations are recommended only if category 1 options are contraindicated.
The International Initiative on Thrombosis and Cancer (ITAC), updated guidelines in 2019, recommends preferred initial treatment with LMWH (GFR ≥30 mL /min) at least for 5-10 days,then can be switched to Edoxaban or Rivaroxaban provided the low risk of GI bleed. In case of renal impairment, alternate agents are heparin or fondaparinux as the initial treatment options.

Conclusion

Most studies show that DOACs effectively prevent and treat CAT and might be a better choice than LMWH. DOAC's are associated with increased risk of bleeding in some studies, particularly in GI and GU malignancies, and are not recommended in these; instead, LMWH should be used. Another limitation with oral anticoagulants is severe renal impairment, and DOAC's are not recommended when Cr Clearance ≤ 30 ml/min. We anticipate the preferred use of oral anticoagulants in the coming years as more data becomes available.

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