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An Update in Anticoagulant Therapy for Patients with Cancer-Associated Venous Thromboembolism

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Abstract

Purpose of Review This review aims to assess the treatment options for cancer-associated venous thromboembolism (VTE) based on the most robust level of evidence recommendations and suggestions based on expert opinion.

Recent Findings Several classes of anticoagulants have been studied in the treatment of cancer-associated thrombosis (CAT). Since the CLOT trial, guidelines recommend the use of low-molecular-weight heparin (LMWH) for the treatment of this condition. However, since 2018, some direct oral anticoagulants became an alternative first-line treatment for CAT. Three Xa antagonists (rivaroxaban, apixaban, and edoxaban) proved to be at least as effective as the LMWH strategy for the short-term prevention of VTE recurrence.

Summary The right choice of treatment in the context of anticoagulation strategy, thrombo-hemorrhagic risk management, and a patient's comorbidities represents a challenge. The correct management of CAT and a more individualized approach are needed to identify risk factors and offer the best treatment for each patient.

Keywords Anticoagulation · Venous thromboembolism · Cancer · Direct oral anticoagulants · Pulmonary embolism

Introduction

Cancer-associated venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary embolism, is the second leading cause of death in patients with malignant disease, second only to the progression of the neoplastic disease [1•]. The association between cancer and VTE is high, and clinically relevant, in several scenarios. VTE may be the first manifestation of cancer [2]. It is believed that approximately 20% of VTE patients have or will have cancer over a short period and that 20% of all cancer patients will present VTE during their clinical course [3]. A recent study showed that the incidence of VTE-revealed occult cancers was 5.3%, but half were already metastasized at diagnosis [2].

Cancer patients have several conditions that predispose them to thrombus generation, such as surgical procedures, immobility due to oncologic pain, blood viscosity, and acquired thrombophilia associated with some kinds of cancer and tumor genetic characteristics like mutations in K-ras, JAK2, or V617F [4–7]. Different cancer types carry different VTE risks. Hematological malignancies and lung, pancreas, stomach, bowel, and brain cancers are associated with a high risk of clot formation [8, 9]. Allied with that, due to longer patient survival, increased detection of incidental VTE during surveillance imaging, and wider use of central venous catheters, the prevalence of cancer-associated thrombosis is increasing [10••]. However, the association of VTE and cancer should not be taken lightly: incidental VTE in cancer patients should be treated the same way as symptomatic VTE in this population, since it is associated with a higher risk of death despite the absence of symptoms [11], and anticoagulation in this setting can improve overall survival [12].

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Cancer patients experience higher rates of VTE recurrence, at least twofold [13], and a higher risk of major bleeding, despite adequate treatment [3, 14]. Cancer-associated venous thromboembolism follows the same principles of VTE treatment, but the patient should be evaluated individually, and some remarks should be emphasized [1•]. Several classes of anticoagulants have been studied in the treatment of cancer-associated thrombosis (CAT), including vitamin K antagonists (VKAs), subcutaneous low-molecular-weight heparin (LMWH), and direct oral anticoagulants (DOACs) [15]. Since the CLOT trial, in 2003, due to 50% reduction in VTE recurrence when compared to VKA treatment of CAT, guidelines recommend the use of low-molecular-weight heparin (LMWH) for the treatment of this condition [16•]. However, since 2018 some direct oral anticoagulants became an alternative first-line treatment for CAT [10••]. The new drugs, tested specifically for CAT, were three Xa antagonists (rivaroxaban, apixaban, and edoxaban) and proved to be at least as effective as the LMWH strategy for the short-term prevention of VTE recurrence [1•], and their predictable anticoagulant activity allows using them at fixed doses and without biological monitoring [17], orally.

In CAT patients, at least 6 months of anticoagulant therapy is preferred in the absence of contraindications. The risk of VTE recurrence remains substantially high after 6 months of therapy, mainly in patients in whom cancer persists, with metastasis, or during chemotherapy [18]. However, the high risk of bleeding in the oncologic population should be considered when the decision of extending the anticoagulant therapy for more than 6 months. Some guidelines advise that the maintenance of anticoagulation stays while cancer is not solved or continuing chemotherapy [3]. Discontinuation may be considered in those whose cancer is no longer active [15].

Parenterally Administered Anticoagulant

Unfractionated Heparin

The initial treatment of VTE with unfractionated heparin (UFH) has been well established for a long time, CAT or no CAT. In 1960, a trial was published that compared anticoagulant therapy with heparin followed by VKA with no therapy in VTE patients. The trial showed that anticoagulation significantly reduced recurrent pulmonary embolism (PE) and mortality [19]. About 30 years later, another trial compared intravenous heparin (intravenous loading dose of 5000 U heparin, followed by an infusion of 1250 U/h for a minimum of 7 days, in combination with VKA acenocoumarol) or to acenocoumarol alone and show the need for initial treatment with a rapid-acting anticoagulant for preventing thrombotic events [20]. Although highly effective, UFH has essential limitations including short half-life, continuous IV infusion, wide interpatient variability, the need for frequent monitoring (activated partial thromboplastin time or anti-factor Xa), and heparin-induced thrombocytopenia, among others [21, 22]. UFH acts as an indirect anticoagulant, potentiating the activity of antithrombin III by inhibiting activated coagulation factors [23], and UFH might be preferred for the initial VTE treatment of the cancer patient with cancer with severe renal impairment (creatinine clearance < 30 mL/min) [22].

Some other alternatives are available when intravenous or subcutaneous medication is chosen as the first anticoagulant therapy of CAT patients, including LMWH or fondaparinux [24]. LMWH is preferred for the first 5–10 days of anticoagulant treatment if there is no severe renal impairment (creatinine clearance < 30 mL/min) [14].

Low-Molecular-Weight Heparin

LMWH has been the standard of care for the initial and long-term treatment of CAT [25, 26]. Due to property, more predictable pharmacokinetics, and bioavailability, the therapy is much simpler and allows for outpatient treatment of many patients,[21]. LMWH requires daily subcutaneous injection, and the therapeutic dosage is based on the patient's weight [16•]. A meta-analysis of 14 trials that include cancer subgroup data showed that LMWH was equivalent to UFH for mortality and clinically suspected deep vein thrombosis (DVT) [27]. On the other hand, in a post hoc analysis that assessed DVT, LMWH was superior to UFH with similar rates of PE and bleeding [21]. Later, one meta-analysis, which included 446 patients with cancer, showed a greater reduction in mortality with LMWH than UFH (OR 0.53, 95% CI 0.33 to 0.85, $p = 0.009$)[28]. Another meta-analysis assessing the first 5–10 days of anticoagulant therapy in patients with cancer compared LMWH with UFH was associated with no significant difference in mortality (RR 0.66, 95% CI 0.40 to 1.10) and VTE recurrence (RR 0.69, 95% CI 0.27 to 1.76) [24].

The treatment regimen with LMWH followed by a VKA has been associated with unsatisfying results in patients with CAT [29, 30]. This patient constitutes a different population when compared to people without cancer in terms of the higher risk of recurrence (10% vs less than 5%) and bleeding, as demonstrated by Prandoni et al. [13]. In the CLOT trial, a pivotal study that defined CAT treatment for 15 years, the safety and efficacy of anticoagulation with the LMWH dalteparin, in comparison to VKA therapy, were evaluated. A total of 676 patients were randomized, and dalteparin was superior to VKA to prevent the recurrence of VTE (8.0% vs 15,8%; HR 0.48, 95% CI 0.30 to 0.77, $p = 0.002$), without an increased risk of bleeding [16•]. Other studies have been conducted and confirm a favorable safety and efficacy profile of LMWH over VKA for the treatment of cancer-associated VTE [31–33]. VKA is preferred for patients with cancer

and severe renal impairment (creatinine clearance < 30 mL/min) [22].

Fondaparinux

Fondaparinux, a subcutaneous Xa inhibitor, can be also used for the initial treatment of CAT. One study comparing fondaparinux with heparin (UFH and LMWH), in this setting, did not show or exclude a beneficial or detrimental effect of fondaparinux on mortality at 3 months (RR 1.25, 95% CI 0.86 to 1.81), recurrent VTE (RR 0.93, 95% CI 0.56 to 1.54) or bleeding (major, RR 0.82, 95% CI 0.40 to 1.66/minor 1.53, 95% CI 0.88 to 2.66) [34]. The use of fondaparinux might be considered for patients with CAT and a history of HIT (heparin-induced thrombocytopenia) [35].

Direct Oral Anticoagulants

Direct oral anticoagulants were introduced for VTE treatment in the general population in 2009 [1•]. Nevertheless, only in 2019, rivaroxaban or edoxaban were recommended as initial options in patients with cancer-associated thrombosis, except in those patients at high risk of gastrointestinal or genitourinary bleeding [10••].

A meta-analysis of a large, direct oral anticoagulant trial considering only included cancer patients ($n = 1132$) suggested that the direct oral anticoagulants were at least as safe and effective as the conventional treatment for VTE in cancer patients [36]. In 2018, with the Hokusai VTE cancer trial, the Xa antagonist, edoxaban, proved to be noninferior to dalteparin as a first-choice treatment in patients with cancer-associated thrombosis for the primary outcome composite of recurrent VTE or major bleeding (12.8% vs 13.5%; HR 0.97, 95% CI 0.70 to 1.36; $p = 0.006$ for noninferiority) [37•]. The excess of major bleeding in the study with edoxaban was confined to patients with gastrointestinal cancer. Thus, edoxaban was a safe and effective therapeutic alternative to LMWH in patients with cancer-associated VTE but requires careful benefit-risk weighting in gastrointestinal cancer.

The first data on rivaroxaban use in active cancer patients was derived from the EINSTEIN-DVT subanalysis, where 462 patients had a cancer diagnosis at study inclusion and 193 received a diagnosis during the study. In none of the cancer subgroups, safety and efficacy outcomes were significantly different between patients receiving rivaroxaban and those receiving VKA, suggesting that anticoagulation with rivaroxaban was at least a feasible treatment option in patients with CAT thromboembolic events [38]. Later, another trial was published (SELECT-D) comparing rivaroxaban with dalteparin in cancer-related DVT, which results were consistent with those of the Hokusai VTE. In the SELECT-D trial, rivaroxaban reduced the rate of recurrent VTE versus dalteparin but at the cost of more bleeding. This trial could not show a significant difference between rivaroxaban and dalteparin concerning major bleeding, but there was a trend toward higher rates of major bleeding with rivaroxaban, especially gastrointestinal bleeds [39•].

More recently, the CASTA DIVA trial, a randomized open-label noninferiority trial, which included patients with active cancer who had proximal VTE, was published and demonstrated that despite the insufficient number of patients to reach the predefined criteria for noninferiority, efficacy, and safety, results were consistent with the previous studies with rivaroxaban [40].

In the AMPLIFY trial, apixaban was compared to enoxaparin followed by warfarin (INR for 2–3) for the treatment of acute venous thromboembolism. Of the 5395 randomized patients, about 10% had active cancer or a history of malignancy. Among patients with active cancer, recurrent VTE occurred in 3.7% and 6.4% of patients in the apixaban and enoxaparin/warfarin groups, respectively (relative risk (RR) 0.56, 95% CI 0.13–2.37); major bleeding occurred in 2.3% and 5.0% of evaluable patients, respectively (RR 0.45, 95% CI 0.08–2.46). The result of the subgroup analysis of cancer patients showed that apixaban could be an interesting option for this category [41].

The first study with apixaban in the cancer-associated VTE population was ADAM VTE, a small pilot study (300 patients) conducted to compare the safety of apixaban and dalteparin for the treatment of VTE. This trial showed that apixaban was associated with low rates of bleeding and VTE recurrence. The primary outcome of major bleeding up to 6 months occurred in none of the patients receiving apixaban and 1.4% of patients receiving dalteparin, with no significant difference. The rate of recurrent VTE was significantly lower in the apixaban group than in the dalteparin group [42]. The CARAVAGGIO trial was a multinational, randomized, investigator-initiated, open-label, noninferiority trial including 1170 patients with cancer and with symptomatic or incidental VTE received apixaban or dalteparin for 6 months, with stratification by symptomatic or incidental VTE and active cancer or history of cancer. For the primary outcome of recurrent VTE at 6 months, apixaban was noninferior to LMWH. Major bleeding and clinically relevant non-major bleeding events were not significantly different between those groups [43•].

Some meta-analysis pooling results from described trials showed that direct oral anticoagulants confer a reduced risk of recurrent VTE (RR 0·62, 95% CI 0·43–0·91), without an increase in major bleeding. DOACs were associated with a substantial increase in the risk of clinically relevant non-major bleeding in all, but one, meta-analysis [44]. One

meta-analysis, focusing on gastrointestinal cancers (483 patients), reported a significantly higher risk of major bleeding in patients receiving direct oral anticoagulants than in patients receiving LMWHs [45].

In addition, the preliminary results of the CANVAS pragmatic randomized trial showed a noninferiority of recurrent VTE treatment efficacy in 811 randomized cancer patients treated with DOACs vs. LMWH. After 6 months, the VTE rates were similar between groups (DOACs, 6.4% vs. LMWH, 7.8%) (HR – 1.3; 95% CI, – 4.4–1.7), with no differences in major bleeding rates (DOACs, 5.4% vs. LMWH, 4.4%) [46].

The main characteristics of the anticoagulant therapies are listed in Table 1.

Special Conditions in CAT Management

In CAT, some conditions need special management, including patients with brain tumors, kidney dysfunction, and thrombocytopenia. The 2022 International Initiative on Thrombosis and Cancer (ITAC) guidelines recommended the use of LMWHs or DOAC for the treatment of established VTE in patients with a brain tumor (grade 2A), based on some studies in which patients with metastatic brain tumors who developed intracerebral hemorrhage had their anticoagulation for VTE evaluated. In these studies, the cumulative incidence of recurrent VTE in brain cancer patients was significantly lower in patients restarting anticoagulation compared with patients who did not restart it [10••, 47]. On the other hand, the results of one meta-analysis of seven retrospective studies (1291 patients) showed that patients with glioma receiving full-dose anticoagulants (LMWH, unfractionated heparin, or vitamin K antagonist) for CAT had an increased risk of intracerebral hemorrhage compared with patients without anticoagulants [48]. Therefore, anticoagulation should be implemented in these patients, with caution.

Thrombocytopenia increases the risk of bleeding complications in patients with CAT [49] and is a common situation in cancer patients. There is limited evidence to guide management in patients with low platelet counts. Guidelines suggest that a therapeutic dose of anticoagulation can be used for patients with a platelet count of ≥ 50,000 platelets/mL [22]. In patients with platelet counts lower than 50,000 platelets/mL, 50% or prophylactic dose LMWH may be used or full-dose anticoagulation with platelet transfusion support may be considered [10••].

Renal failure is another common condition for the cancer patient and the ones presenting CAT. DOACs have distinct rates of renal elimination, ranging from 80% for dabigatran to 30% for the various Xa antagonists [50]. In patients with renal impairment, data from the CARAVAGGIO trial suggested that apixaban may be safe for the CAT treatment in moderate renal impairment since it did not demonstrate significant differences in the rates of major bleeding in patients with creatinine clearance of 30–80 mL/min treated with apixaban or LMWH [43•]. Despite those possibilities, the latest ITAC guidelines suggest the use of unfractionated heparin followed by early vitamin K

Table 1 Main characteristics of the anticoagulant therapies

Drug	LMWH	VKA	Rivaroxaban*	Apixaban*	Edoxaban*
Mechanism of action	Inhibition of Xa factor binding to AT III	Inhibition of vitamin K-dependent clotting factors (II, VII, IX, X)	Direct anti-Xa	Direct anti-Xa	Direct anti-Xa
Onset of action	3–5 h	36–72 h	2–4 h	1–3 h	1–2 h
Half-life	3–7 h	S- and R-warfarin 32 and 42 h	7–13 h	8–15 h	9–11 h
Dose	1 mg/kg twice daily * 1 mg/kg once daily for renal impairment creatinine clearance < 30 mL/min	2.5–5 mg daily until INR between 2.0 and 3.0	15 mg twice daily for 3 weeks and then 20 mg once daily	10 mg, twice daily for 7 days, and then 5 mg twice daily	60 mg once daily (following initial 5–10 days of LMWH) * 30 mg once daily (following initial 5–10 days of LMWH) for renal impairment creatinine clearance 30–50 mL/min
Route of elimination	Renal	Hepatically metabolized	70% renal	25% renal	35% renal

*DOACs are not recommended when creatinine clearance < 15 mL/min or dialysis

LMWH low-molecular-weight heparin; *VKA* vitamin K antagonists; *AT III* antithrombin

antagonists (possible from day 1) or LMWH adjusted to anti-Xa concentration for the treatment of established VTE [10••] to patients with CAT and renal impairment.

Apixaban and rivaroxaban are contraindicated in hepatic disease associated with coagulopathy and clinically relevant risk. However, DOACs can be used in patients with moderate liver insufficiency, though dosage adjustment is necessary. In cases of severe hepatic impairment (e.g., Child–Pugh class C) and cirrhotic patients with Child–Pugh B or C, rivaroxaban should not be administered [51]. Apixaban should be used with caution in patients with mild or moderate hepatic impairment (Child–Pugh class A or B). With edoxaban, patients with Child–Pugh class A or B exhibited comparable pharmacokinetics and pharmacodynamics to healthy controls. Despite this possibility, it is worth mentioning that this population was always excluded from clinical trials [52].

Gut absorption of DOACs should be considered if these drugs are the ones chosen for CAT therapy. Absorption of DOACs is dependent on the P-glycoprotein (P-gp) efflux pump, and Xa antagonists are also substrates for CYP3A4 [17]. This may be particularly relevant to patients submitted to surgeries, such as gastrectomy. The site of absorption throughout the GI tract is different for each DOAC. Rivaroxaban is absorbed by the stomach and proximal intestine, edoxaban by the proximal small intestine, and apixaban in the distal bowel or ascending colon [15]. Although there is limited evidence of the use of DOACs in patients with a reduction in GI absorptive surface, whether, by surgery or other disorders, they should be avoided, and it is reasonable to consider LMWH [15, 17, 53].

All DOACs are substrates of P-glycoprotein (P-gp), and apixaban and rivaroxaban are also substrates of CYP3A4, so therapies that affect P-gp or CYP3A4 metabolism have the potential to interact with DOACs. Numerous anticancer therapies are inhibitors or inducers of the P-gp and/or CYP3A4 pathways, with the potential to interact with DOACs [54]. Analysis of the effects of concomitant administration of anticancer agents, including antiangiogenic monoclonal antibodies and anticancer agents known to be inhibitors or inducers of P-gp and/or CYP3A4, did not appear to influence the incidence of VTE recurrence and major bleeding associated with apixaban in the CARAVAGGIO study, suggesting that apixaban can be administered in patients with CAT receiving anticancer treatment [43•, 55]. Dose reduction to 2.5 mg twice daily is recommended for apixaban in patients receiving concurrent strong dual CYP3A4 and P-gp inhibitors and to 30 mg daily for edoxaban in patients on concurrent potent P-gp inhibitors, while avoidance is recommended for other DOACs [56].

The algorithm for choosing anticoagulant therapy in cancer-associated thrombosis, including special conditions, is shown in Fig. 1.

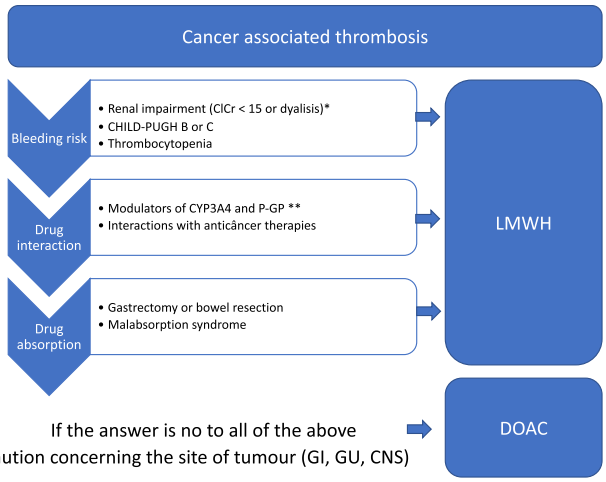

Fig. 1 Algorithm for choosing anticoagulant therapy in cancer-associated thrombosis

How Long Should We Anticoagulate a CAT Patient?

That is still a matter of debate. After the acute phase of VTE (3–6 months), it is reasonable to extend the anticoagulant regimen for CAT patients with a high risk of recurrence, until 12 months or longer. Indeed, the trials investigating the management of secondary prevention after venous thrombotic events are the RE-MEDY and RE-SONATE [57], EINSTEIN-EXT [58], EINSTEN-CHOISE [59], and Amplify-EXT [60] trials, which evaluate the efficacy of DOACs in preventing recurrent venous thrombosis after 6 months. In the RE-MEDY and RE-SONATE trials [57], dabigatran vs. warfarin or placebo, respectively, showed a reduction of recurrent VTE with similar rates of major bleeding. In the EISTEIN-EXT [58] and EINSTEIN-CHOISE [59] trials, rivaroxaban reduced the risk of recurrent VTE without a difference in major bleeding rates compared to placebo or aspirin, respectively; in the Amplify-EXT trial, apixaban showed the same results versus placebo. However, active malignancies were considered an exclusion criterion in these trials; therefore, these results cannot be extrapolated to the oncologic population [3, 61]. The permanent discontinuation of anticoagulation was proposed, in a recent study, for patients with CAT when there is severe persistent thrombocytopenia, prior history of major bleeding or ongoing bleeding without curative options, absence of risk factors for VTE recurrence, or in the terminal phase of the malignancy as the risk of bleeding is substantial [18]. However, in the absence of clear-cut data, this approach should be undertaken on a case-by-case basis with substantial thought on what is in the patient's best interest.

Vena Cava Filter

The applicability of vena cava filters (VCF) is uncertain and controversial. Inferior vena cava filters might be considered if anticoagulant treatment is contraindicated, but there are no randomized clinical trials to guide therapy with filters in this population [10••]. Some trials in patients with cancer suggest higher rates of recurrent VTE and the absence of survival advantage with filters [14]. Another retrospective study compared the use of VCF in 247 patients with cancer, in whom anticoagulant therapy was contraindicated, with 247 patients with cancer without VCF reporting a non-significant lower risk of death (12.2% vs 17.0%, $p = 0.13$) and a significantly lower risk of pulmonary embolism-related mortality (0.8% vs 4.0%, $p = 0.04$) [62]. Further studies are needed.

Thrombolysis

Data about thrombolytic therapy in patients with CAT are lacking [10••]. The decision about parenteral or catheter-directed thrombolysis must be done on a case-by-case basis, especially in patients with brain metastasis, considering the risk of immediate death of the CAT patient versus the risk of bleeding. Catheter-directed thrombolysis may be an alternative for the management of high-risk death patients with CAT since in theory the risk of bleeding during these procedures is lower; however, efficiency and safety data in CAT patients are lacking.

Conclusion

Cancer-related VTE is a common clinical manifestation of the malignant disease and has a multifactorial pathogenesis. The right choice of treatment, with consideration of a thoughtful anticoagulation strategy, thrombo-hemorrhagic risk management, and assessment patient's comorbidities, represents a challenge for physicians. Early identification and treatment of this complication are particularly relevant in the onco-hematologic setting, given the substantial impact of venous thrombotic events on morbidity and mortality. The first line of treatment now includes LMWH and DOACs. Indeed, despite evidence of increased risk of bleeding in specific cases, DOACs are an attractive alternative to LMWH in the treatment of VTE in cancer patients, especially those without drug interactions and those with significantly impaired renal function.

Data Availability The authors declare that the data supporting the findings of this study are available within the article.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest The authors declare no competing interests.

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Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

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