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How I treat cancer-associated thrombosis

Florian Moik,[1] Ingrid Pabinger,[1] Cihan Ay [1,2]

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[1]Clinical Division of Haematology and Haemostaseology, Department of Medicine I, Comprehensive Cancer Center Vienna, Medical University of Vienna, Vienna, Austria
[2]I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia

Correspondence to
Dr Cihan Ay;
cihan.ay@meduniwien.ac.at

ABSTRACT

Patients with cancer are at an increased risk of symptomatic venous thromboembolism (VTE). In addition, an increasing number of patients with incidental thromboembolic events have been recorded in clinical practice. Therapeutic anticoagulation is crucial to prevent thrombus progression and reduce risk of recurrence; however, this comes at the price of an increased bleeding risk, which necessitates a personalised approach to choose the most appropriate type of therapy. Over the last decade, low-molecular-weight heparin has been the preferred anticoagulant agent for patients with cancer-associated thrombosis due to better efficacy and similar safety profile compared with vitamin K antagonists. While direct oral anticoagulants (DOAC) have emerged as new option for treatment of VTE in a general population, only limited data have been available specifically for patients with cancer until recently. Randomised, controlled trials have now been published, establishing DOAC as an alternative for the treatment of cancer-associated thrombosis. However, the improvement in the therapeutic armamentarium is accompanied by a number of special considerations. For instance, risk of bleeding is elevated in patients with cancer-associated VTE receiving DOAC, especially in certain tumour types (eg, gastrointestinal), and no guidance exists regarding their use in patients with severe thrombocytopaenia. Furthermore, DOAC are prone to certain drug–drug interactions and their effect might be altered due to nausea and vomiting in patients receiving chemotherapy. Here, we provide guidance on how to treat cancer-associated VTE and how new evidence from randomised controlled trials can be implemented in clinical practice. There are still clinical scenarios where robust evidence is lacking and treatment recommendations are based on extrapolations from other populations or expert opinion only. Therefore, additional research in special subpopulations is needed to optimise management of patients in challenging clinical scenarios.

VENOUS THROMBOEMBOLISM IN PATIENTS WITH CANCER

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in patients with cancer. The incidence of VTE in patients with cancer is elevated compared with the general population, with reported annual rates in a pooled analysis of 38 cohort studies between 0.5% and 20%, depending on specific cancer subpopulation, compared with an annual incidence rate of 0.1%–0.2% in patients without cancer.[1 2] In addition, thrombosis at unusual sites, such as in the splanchnic veins, or related with a central venous catheter (CVC) is frequently observed in patients with cancer.

Cancer-associated thromboembolism (CAT) causes increased morbidity, sometimes delay of oncological treatment and an increase in healthcare expenses.[3–5] Furthermore, VTE is among the leading causes of death in patients with cancer and the occurrence of thrombotic events is a negative prognostic factor beyond direct VTE-related mortality, underlining the complex interaction between the haemostatic system and malignancy.[6–8]

Therapeutic anticoagulation in patients with cancer-associated VTE requires carefully balancing risk and benefit. The management of patients with CAT is challenged by a higher risk of both recurrent VTE and bleeding events compared with patients with VTE without cancer, and oral anticoagulation can be further complicated by severe thrombocytopaenia, potential drug–drug interactions and nausea and vomiting.[9 10]

Here, we provide a concise overview on newly published randomised controlled trials, on how most recent evidence has been incorporated in updated guidelines for treatment of VTE in patients with cancer and our approach to patients with cancer-associated VTE. We also discuss several special issues and clinical scenarios, such as potential drug interactions of direct oral anticoagulants (DOAC), management of anticoagulation in patients with severe thrombocytopaenia, incidentally diagnosed asymptomatic VTE and catheter-related thrombosis (CRT).

ANTICOAGULATION IN PATIENTS WITH ACUTE CANCER-ASSOCIATED VTE

In the past two decades, the recommended treatment for patients with cancer and acute VTE in international guidelines was low-molecular-weight heparin (LMWH). This has been based on the pivotal CLOT trial, comparing LMWH (dalteparin) to vitamin

K antagonists (VKA), that found lower rates of recurrent VTE at 6 months (9% vs 17%; HR: 0.48; 95% CI 0.30 to 0.77) and a similar risk of bleeding events (6% vs 4%, p=0.27) in patients treated with dalteparin.[11] Treatment and secondary prevention of patients with VTE in a general population has been revolutionised by the development and introduction of DOAC in clinical practice. However, patients with cancer were underrepresented in clinical trials evaluating the efficacy and safety of these agents against VKA and details on their cancer status were not clearly defined.[12–15] In a meta-analysis, including subgroups of patients with cancer from phase III trials comparing DOAC to VKA, efficacy and safety were comparable.[16] However, as the comparative agent in these studies was VKA, which was not the preferred agent in patients with cancer according to guideline recommendations, only limited clinical implications could be drawn.

In 2018, the results of two phase III trials have been published, which specifically aimed at testing the efficacy and safety of DOAC against LMWH for the treatment of CAT. The Hokusai VTE cancer trial, a prospective, open label, blinded endpoint evaluation (PROBE), non-inferiority trial, compared edoxaban, a direct coagulation factor Xa inhibitor, to anticoagulation therapy with dalteparin for a treatment duration of 6–12 months. The primary outcome, a composite of recurrent VTE and major bleeding events (according to ISTH (International Society on Thrombosis and Haemostasis) definition) at 12 months, did not differ between edoxaban and dalteparin (edoxaban: 12.8%; LMWH: 13.5%; HR: 0.97; 95% CI 0.70 to 0.36, p=0.006 for non-inferiority). Patients treated with edoxaban experienced fewer VTE events (7.9% vs 11.3%; HR: 0.71; 95% CI 0.48 to 1.06), but rates of major bleeding were higher (6.9% vs 4.0%; HR: 1.77; 95% CI 1.03 to 3.04), mainly due to an excess of gastrointestinal (GI) bleeding in patients with GI malignancies.[17] In SELECT-D, an open label, pilot study, rivaroxaban, also a direct factor Xa inhibitor, was compared with LMWH (dalteparin) for the treatment of cancer-associated VTE. The 6-month cumulative incidence of recurrent VTE was lower in patients treated with rivaroxaban (4% vs 11%, HR: 0.43; 95% CI 0.19 to 0.99) and the incidence of major bleeding was higher (6% vs 4%, HR: 1.83; 95% CI 0.68 to 4.96), as was the rate of clinically relevant non-major bleeding (CRNMB) (13% vs 4%, HR: 3.76; 95% CI 1.63 to 8.69), comprising mostly of upper GI and urothelial bleeding.[18] Also in the SELECT-D study, GI bleeding tended to be higher in patients with gastro-oesophageal and colorectal cancer. Recruitment of patients with upper GI malignancy (oesophageal cancer and cancer of the gastro-oesophageal junction) was terminated during the ongoing SELECT-D trial, due to a non-significant rise in major bleeding events.[18] Importantly, risk of intracranial bleeding in both the HOKUSAI VTE cancer and SELECT-D study in patients receiving a DOAC was not increased. Fatal bleeding occurred in one patient each in patients receiving rivaroxaban and dalteparin in SELECT-D, no patient in the edoxaban group and two patients in the dalteparin group in the Hokusai VTE cancer trial.[17 18]

In 2019, results from the ADAM-VTE trial have been published, comparing the oral factor Xa inhibitor apixaban to dalteparin for the treatment of cancer-associated VTE, including upper extremity and splanchnic vein thrombosis (SVT). The primary outcome event of major bleeding (according to ISTH definition) occurred in 0% of 145 patients in the apixaban group and 1.4% of 142 patients in the dalteparin group. Secondary outcomes included recurrent VTE, with rates significantly lower in the apixaban arm compared with the dalteparin arm (0.7% vs 6.3%, HR: 0.099; 95% CI 0.013 to 0.780).[19] The frequency of CRNMB was 6% in both groups. Interestingly, the rate of major bleeding, recurrent VTE and mortality in the LMWH arm in the ADAM-VTE trial was lower compared with the LMWH arm in the Hokusai VTE cancer and SELECT-D studies, suggesting that a lower risk population was included in the ADAM-VTE study. A large randomised controlled non-inferiority trial comparing apixaban to LMWH (dalteparin) for treatment of acute cancer-associated VTE, the CARAVAGGIO study, which is ongoing, will provide further evidence for efficacy and safety of apixaban for treatment of cancer-associated VTE.[20]

Based on these studies, anticoagulation with either edoxaban or rivaroxaban has been incorporated in updated guidelines for management and treatment of cancer-associated VTE as alterative to LMWH.[21–23] At the time of publication of these guidelines, the full publication of the ADAM VTE trial was not available to expand the recommendation also to apixaban. However, several factors have to be considered prior to deciding on treating a patient with a DOAC. In figure 1, we provide a treatment algorithm, which is based on evidence from interventional trials but also on expert opinion because of limited available data. The suggestions should help to guide the clinical decisions in daily practice, with particular value on patients' safety. Furthermore, VKA might still be a treatment option for patients with no access or contraindications to DOAC and LMWH.[22] As for these reasons, VKA are still frequently used in many parts of the world and knowledge and skills in VKA management, in particular dose adjustment and monitoring, are still important.

The advantage of DOAC lies in its oral administration and easy, standardised dosing and thereby might enhance patient compliance. LMWH is favourable due to experience in use in this setting and its applicability in patients with contraindications to DOAC. VKA can be administered if both LMWH and DOAC are contraindicated and is an economical, globally more easily available alternative for anticoagulation in patients with CAT.

Table 1 summarises the phase III and observational studies on the safety and efficacy of different anticoagulation strategies in patients with cancer and acute VTE.

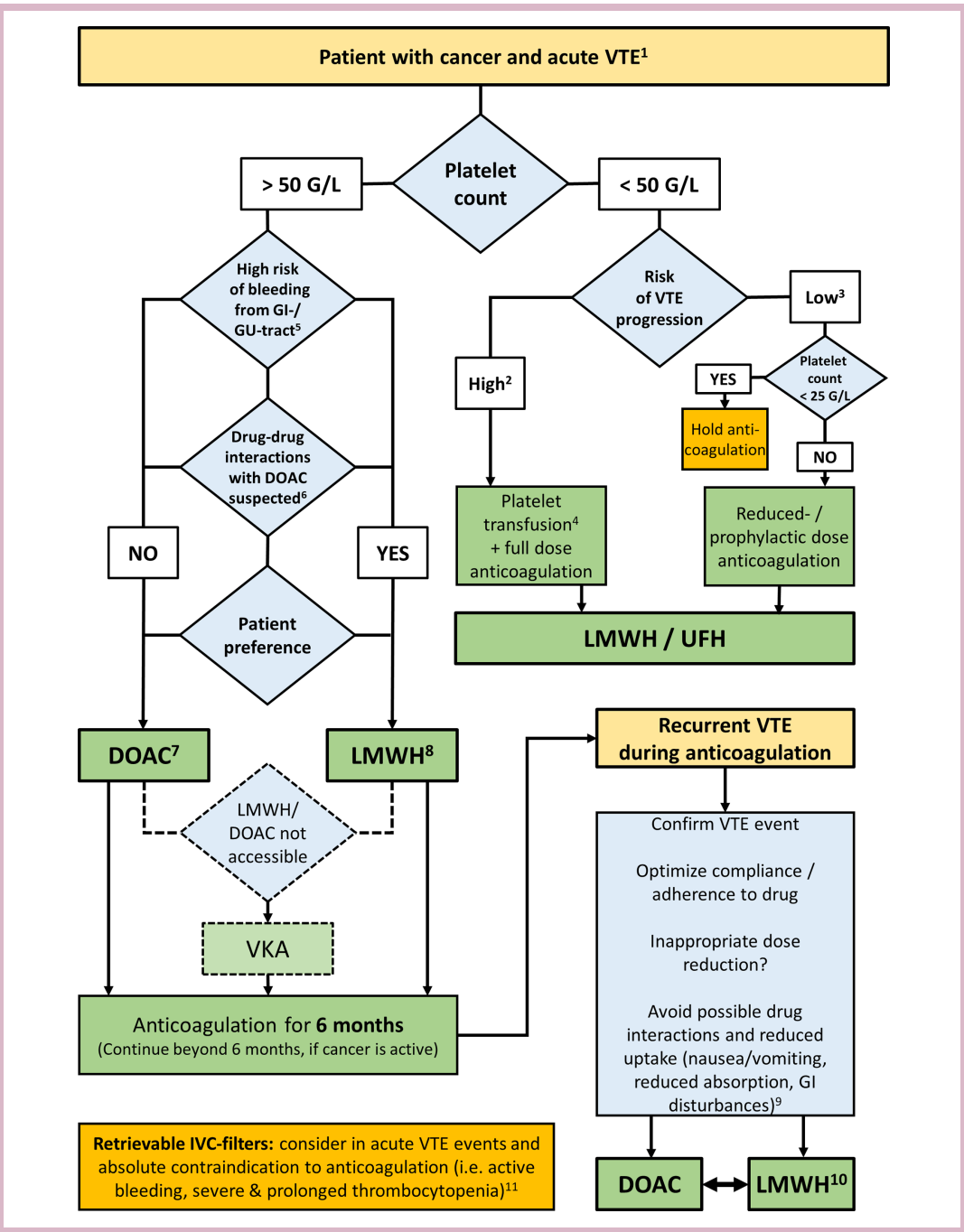

Figure 1 **Treatment algorithm for patients with cancer and acute VTE;** [1]: VTE including symptomatic and incidentally detected events (excluding isolated, asymptomatic subsegmental pulmonary embolism); [2]: high risk: symptomatic, proximal PE, proximal DVT or history of previous thrombotic events in acute phase of VTE (<30 days since diagnosis of the event); [3]: low risk: distal DVT, incidental subsegmental PE, CRT and/or patients in subacute phase of VTE (>30 days since event); [4]: target platelet count for transfusion: 40–50 G/L; [5]: luminal GI tumours (intact primary tumour), tumours at risk of bleeding from GU tract, nephrostomy tubes, active GI mucosal abnormalities (gastric/duodenal ulcer, gastritis, colitis, esophagitis, etc); [6]: strong interaction with CYP3A4 or P-gp suspected; [7]: DOAC: edoxaban: 60 mg once daily after LMWH lead-in (reduced dose of 30 mg once daily: creatinine clearance below 50 mL/min, body weight of <60 kg or concomitant use of a potent P-glycoprotein (P-gp) inhibitor); rivaroxaban: 15 mg twice daily for 3 weeks, then 20 mg once daily; apixaban: 10 mg twice daily for 7 days, followed by 5 mg twice daily; [8]: dalteparin: 200 IU/kg daily during the first month, then 150 IU/kg daily; [9]: rivaroxaban absorption reduced when not taken with food; [10]: for patients treated with LMWH: switch to DOAC or escalate dose; [11]: retrievable IVC filters represent an option until anticoagulation is possible only in very selected cases depending on thrombus location (ie, proximal DVT) and timing since VTE diagnosis according to guidance from the ISTH SSC.[25] **Abbreviations**: DVT, deep vein thrombosis; DOAC, direct oral anticoagulant; IVC, inferior vena cava; GI, gastrointestinal; GU, genito-urinary; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism; VKA, vitamin K antagonist.

Table 1 Summary of randomised controlled trials on anticoagulation in patients with cancer-associated VTE

Concept	LMWH versus VKA				DOAC versus LMWH		
Trial name	**Canthanox**	**CLOT**	**Oncenox**	**Catch**	**Hokusai-VTE cancer**	**SELECT-D**	**ADAM-VTE**
First author & year of publication	Meyer, 2002[43]	Lee, 2003[11]	Deitcher, 2006[44]	Lee, 2015[45]	Raskob, 2018[17]	Young, 2018[18]	McBane, 2019[19]
Study drug (dose)	**LMWH (enoxaparin)** (1.5 mg/kg 1x/d)	**LMWH (dalteparin)** (200 IU/kg 1x/d 1 month → 150 IU/kg 1x/d)	**LMWH (enoxaparin)** (1/1.5 mg/kg 1x/d after 1 mg/kg 2x/d for 5d)	**LMWH (tinzaparin)** (175 IU/kg 1x/d)	**Edoxaban** (60 mg 1x/d after LMWH for 5d)*	**Rivaroxaban** (15 mg 2x/d 3 weeks → 20 mg 1x/d)	**Apixaban** (10 mg 2x/d 7 days → 5 mg 2x/d)
Comparator (dose)	**VKA (Warfarin)** (target INR: 2–3 after LMWH for min. 4d)	**VKA (Warfarin/ Acenocoumarol)** (target INR: 2.5 after LMWH for 5–7d)	**VKA (Warfarin)** (target INR: 2–3 after LMWH for min. 5d)	**VKA (Warfarin)** (target INR 2–3 after LMWH for 5–10d)	**LMWH (dalteparin)** (200 IU/kg 1x/d 1 month → 150 IU/kg 1x/d)	**LMWH (dalteparin)** (200 IU/kg 1x/d 1 month → 150 IU/kg 1x/d)	**LMWH (dalteparin)** (200 IU/kg 1x/d 1 month → 150 IU/kg 1x/d)
Qualifying VTE diagnosis	Pulmonary embolism and/ or deep venous thrombosis	Acute, symptomatic proximal deep-vein thrombosis, pulmonary embolism	Acute symptomatic venous thromboembolic events	Acute, symptomatic proximal deep vein thrombosis and/or pulmonary embolism	Acute symptomatic/ incidental DVT (popliteal, femoral, iliac vein or IVC; acute, symptomatic PE confirmed by imaging; incidentally detected PE of segmental or more proximal pulmonary arteries)	Symptomatic lower-extremity proximal DVT, symptomatic PE, or incidental PE	Acute lower and upper extremity (jugular, innominate, subclavian, axillary, brachial) DVT, PE, splanchnic† or cerebral vein thrombosis
Relevant exclusion criteria	–	Incidental VTE	CRT, eligibility for curative surgery	Asymptomatic VTE	–	–	–
Primary outcome	Composit: recurrent VTE +major bleeding	Recurrent VTE	Feasibility of recruitment and patient compliance	Recurrent VTE	Composit: recurrent VTE +major bleeding	Recurrent VTE	Major bleeding
Study population	146	676	101 (ITT:91)	900	1050 (PP: 1046)	406 (PP: 402)	300 (primary analysis: 287)
Duration	3 months	6 months	6 months	6 months	12 months	6 months	6 months
Rate of **recurrent VTE** (SD vs C)	**2.8%** vs **4.0%** (2/71 vs 3/75) n.r.	**9%** vs **17%** (27/336 vs 53/336) HR 0.48 [0.30–0.77]	**6.6%** vs **10.0%** (4/61 vs 3/30) n.r.	**7.2%** vs **10.5%** (31/449 vs 45/451) HR 0.65 [0.41–1.03]	**7.9%** vs **12.3%** (41/522 vs 59/524) HR 0.71 [0.48–1.06]	**4%** vs **11%** (8/203 vs 18/203) HR 0.43 [0.19–0.99]	**0.7%** vs **6.3%** (1/145 vs 9/142) HR 0.099 [0.013–0.780]
Rate of **major bleeding** (SD vs C)	**7.0%** vs **16.0%** (5/71 vs 12/75) p=0.09	**6%** vs **4%** (19/338 vs 12/335) p=0.27	**9.0%** vs **2.9%** (6/67 vs 1/34) n.r.	**2.7%** vs **2.4%** (13/449 vs 12/451) HR 0.89 [0.40–1.99]	**6.9%** vs **4.0%** (36/522 vs 21/524) HR 1.77 [1.03–3.04]	**6%** vs **4%** (11/203 vs 6/203) HR 1.83 [0.68–4.96]	**0.0%** vs **1.4%** (0/145 vs 2/142) HR not estimable
CRNMB (SD vs C)	–	–	–	**10.9%** vs **15.3%** (49/449 vs 69/451) HR 0.58 [0.40–0.84]	**14.6%** vs **11.1%** (76/522 vs 58/524) HR 1.38 [0.98–1.94]	**13%** vs **4%** (25/203 vs 7/203) HR 3.76 [1.63–8.69]	**6.2%** vs **6.3%** (9/145 vs 9/142) HR 0.931 [0.43–2.02]
Any bleeding (SD vs C)	10/71 vs 21/75	14% vs 9%	**67.2%** vs **52.9%** (45/67 vs 18/34)	–	–	–	–

Continued

Table 1 Continued

Concept	LMWH versus VKA				DOAC versus LMWH		
Trial name	**Canthanox**	**CLOT**	**Oncenox**	**Catch**	**Hokusai-VTE cancer**	**SELECT-D**	**ADAM-VTE**
Comment on bleeding events	Six deaths attributed to bleeding in warfarin group, none in dalteparin group	–	–	–	MB: mostly non-severe upper GI in patients with upper GI cancer	More MB in patients with upper GI cancer Most CRNMBs were GI or GU	–
Mortality (SD vs C)	**11.3%** vs **22.7%** p=0.07	**39% vs 41%** 130/336 vs 136/336 p=0.53	**32.8%** vs **32.4%** 22/67 vs 11/34 n.r.	**34.7%** vs **32.2%** 150/449 vs 138/451 HR 1.08 [0.85–1.36]	**39.5%** vs **36.6%** 206/522 vs 192/524 HR 1.12 [0.92–1.37]	**25%** vs **30%** 48/203 vs 56/203 n.r.	**16%** vs **11%** (23/145 vs 15/142) HR 1.40 [0.82–2.43]

*Edoxaban reduced dose of 30 mg once daily when creatinine clearance was below 50 mL/min, body weight of <60 kg or concomitant use of a potent P-glycoprotein (P-gp) inhibitor.
†Splanchnic vein thrombosis including hepatic, portal, splenic, mesenteric, renal and gonadal vein thrombosis.
C, comparator; CRNMB, clinically relevant non-major bleeding;CRT, catheter-related thrombosis; DOAC, direct oral anticoagulant; GI, gastrointestinal; GU, genito-urinary; ITT, intention-to-treat population; IVC, inferior vena cava;LMWH, low-molecular-weight heparin; n.r., not reported; PP, per-protocol population; SD, study drug; VKA, vitamin K antagonist; VTE, venous thromboembolism.

PRACTICAL CONSIDERATIONS OF DOAC USE IN PATIENTS WITH CANCER

Tumour types with high bleeding risk

In patients with CAT treated with a DOAC, more bleeding events in certain subpopulations were observed. Therefore, an individual risk–benefit evaluation is needed and their uncritical use should be avoided. The risk of bleeding seems to be increased in colorectal and gastro-oesophageal cancers and possibly also genito-urinary cancers. Therefore, in patients with luminal GI cancer with the primary tumour in place, tumours at risk of bleeding from the genito-urinary (GU) tract, nephrostomy tubes or active GI mucosal abnormalities (eg, gastric/duodenal ulcer, gastritis, colitis, esophagitis) DOAC are not suggested as the first-line treatment option.[21 22]

Frail patients

SELECT-D, Hokusai VTE cancer and ADAM-VTE have included patients with Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 and therefore, data derived from these studies might not be generalisable to frail patients or those with unfavourable performance status.[17 18]

Thrombocytopaenia

Another common factor influencing the individual risk of bleeding is the presence of thrombocytopaenia, which complicates treatment of CAT. Despite the substantial risk of bleeding in patients with cancer and thrombocytopaenia, rates of recurrent VTE are not reduced. For patients with cancer, acute VTE and platelet counts above 50 G/L, full-dose anticoagulation, either with LMWH or DOAC, can be administered. As suggested in a guidance document by an international expert group, for patients with cancer-associated VTE with platelet counts between 25 and 50 G/L, two possible strategies can be followed, depending on the underlying risk of VTE progression: (1) for patients with high-risk VTE features such as symptomatic, proximal PE, proximal DVT or history of previous thrombotic events who are in the acute phase of VTE (<30 days since diagnosis of the event), full-dose anticoagulation with LMWH or unfractionated heparin (UFH) in combination with platelet transfusion to keep thrombocyte counts above 40–50 G/L is suggested. (2) For patients with low risk of VTE progression (distal DVT, incidental subsegmental PE, CRT and/or patients in the subacute phase of VTE (>30 days since event), anticoagulation with half-therapeutic or prophylactic dose of LMWH is suggested. Anticoagulation should be withheld temporarily for patients with platelet counts below 25 G/L and resumed in full dose above 50 G/L. There is no clear guidance for use of DOAC in patients with severe thrombocytopaenia. As supported by the Hokusai VTE cancer study, DOAC can be used in patients with a platelet count >50 G/L and should be paused when platelets drop <50 G/L, and switching to LMWH should be considered on a case-by-case basis.[24 25] In patients with acute VTE and absolute contraindications for anticoagulation,

including active haemorrhage and severe, prolonged, transfusion resistant thrombocytopaenia, retrievable inferior vena cava (IVC) filters might be considered in very selected cases until anticoagulation can safely be initiated, depending on type of VTE event (ie, proximal DVT) and time since diagnosis, with increasing interval arguing against its usage.[25] The authors suggest a conservative approach towards the application of IVC filters in this setting.

Drug–drug interactions

Risk of bleeding and efficacy can further be influenced by *drug–drug interactions*. DOAC are substrates of the P-glycoprotein (P-gp) and are in part metabolised through CYP3A4. Therefore, their plasma levels can be altered by a variety of drugs, especially some anti-cancer drugs that interfere with CYP3A4 or P-gp. LMWH is the suggested alternative in patients with suspected strong interactions, as patients with concomitant use of certain drugs that strongly influence CYP3A4 or P-gp have been excluded from inclusion to Hokusai VTE cancer and SELECT-D.[26] Drugs that might influence efficacy and safety of DOAC comprise both antineoplastic agents (eg, paclitaxel, certain tyrosine kinase inhibitors, bicalutamide, enzalutamide, abiraterone) and supportive care medication (eg, dexamethasone, prednisone, azol antifungals, neurokinin-1 antagonists). However, the clinical impact of these suspected interactions is unknown as pharmacodynamics, pharmacokinetic and clinical outcome studies are not available.[27]

Nausea and vomiting

A common problem in patients with cancer that might also contribute to alterations in DOAC bioavailability is *nausea and vomiting*, influencing uptake of orally administered drugs. It is suggested to optimise antiemetic therapy and to temporarily switch anticoagulation to parenteral routes (eg, LMWH) in the case of both prolonged vomiting episodes (>24 hours) or acute episodes (<24 hours) and to resume DOACs after the episodes have resolved.[28] This scheme might ensure consistent anticoagulation in a patients with VTE and nausea and vomiting.

Altered GI anatomy

Patients with cancer often undergo surgical procedures which result in anatomic changes and might affect GI absorption of DOAC, such as total/partial gastrectomy, Roux-en-Y gastric bypass (RYB) or colectomy.[29] Because of the location of absorption of rivaroxaban, which is predominantly in the stomach, total gastrectomy might affect its bioavailability.[30] The effect of partial gastrectomy and RYB are uncertain. Apixaban is mainly absorbed in the proximal small bowel.[31] Its bioavailability is probably less affected by gastric resection and possibly reduced by colectomy. Levels of edoxaban, on the other hand, are possibly reduced in patients with a history of gastric resection and RYB and unlikely affected in patients who underwent colectomy.[29 32] In the absence of dedicated studies assessing the efficacy of DOAC after GI resection or bypass in patients with cancer, most statements are based on extrapolations from data on physiology of DOAC absorption, case reports and case series of patients mainly in bariatric surgery.[29 33]

DURATION OF ANTICOAGULATION

Patients with cancer-associated VTE and indication for anticoagulation should preferably be treated for 6 months.[22] Duration of anticoagulation should be extended in patients with ongoing active malignancy, for example in metastatic disease, and/or ongoing antineoplastic therapy and should be reassessed periodically for its risk–benefit ratio.[21–23 34]

SPECIAL CLINICAL EVENTS

In addition to balancing risk of bleeding and recurrent VTE according to underlying risk factors such as type of malignancy, low platelet counts and potential drug–drug interactions, some special clinical scenarios of cancer-associated thrombosis need special consideration prior to deciding on a specific therapeutic approach.

Catheter-related thrombosis

Patients with cancer often receive antineoplastic therapy via CVCs, which pose a significant risk of CRT. However, evidence on therapeutic management of these events is limited. A retrospective multi-centre analysis of therapeutic strategies in CRT revealed that treatment approaches in clinical practice are heterogeneous, with a significant percentage of patients (16%) who do not receive anticoagulation but rather are being treated with removal of the catheter alone.[35] According to guidelines, patients with CRT are suggested to undergo anticoagulation for a minimum of 3 months and as long as the CVC remains in situ.[22] Preferably, LMWH should be used, as only very limited data exist on the use of DOACs in this setting. Based on expert opinion, the catheter may remain in place in the absence of infection, malfunction and incorrect positioning, and if it is planned to continue to use the catheter. Removal of the CVC without the administration of anticoagulation can be done in patients with high risk of or active bleeding.[36]

Incidental PE

Due to regular restaging procedures in patients with cancer, incidentally detected, asymptomatic PE is a dilemma to manage. Despite its asymptomatic presentation, cohort studies found a similar risk of recurrence in patients with incidental VTE compared with symptomatic events.[37] Therefore, anticoagulation should be initiated in patients with (i) clinical features of VTE who then cannot be classified as truly 'asymptomatic', (ii) PE involving the segmental or more proximal pulmonary arterial branches or multifocal subsegmental branches and (iii) PE of a single subsegmental branch who are found to have accompanying asymptomatic proximal

DVT. For patients with isolated, subsegmental, asymptomatic, independently confirmed PE with or without distal DVT, a case-by-case decision (anticoagulation or close clinical monitoring) can be followed.[38]

Splanchnic vein thrombosis

Thrombosis of the portal, mesenteric or splenic veins, summarised as SVT, either symptomatic or incidentally discovered on imaging procedures, can complicate management in patients with cancer, with the highest risk in patients with hepatocellular cancer, cholangiocarcinoma or pancreatic cancer.[39] Furthermore, direct tumour ingrowth into splanchnic vessels, also known as tumour thrombus, consisting solely on antineoplastic proliferation, most frequently observed in renal cell carcinoma, might mimic 'real' SVT.[40] In patients with confirmed symptomatic SVT, excluding tumour thrombus by imaging, continuous anticoagulation with LMWH over VKA is recommended for a minimum of 3 months or longer for patients with persistent thrombotic risk.[41 42] For patients with asymptomatic SVT, anticoagulation remains controversial, with only very limited data to support either strategy. Therefore, a case-by-case decision considering individual risk of bleeding and recurrence has to be made.[23 41 42]

CONCLUSIONS

Clinical management of cancer-associated thrombosis is a challenging, multilayered issue. The therapeutic armamentarium has broadened by emerging evidence on the safety and efficacy of DOAC (figure 1). In general, we treat patients with active cancer and newly diagnosed symptomatic or incidental VTE with DOAC, if they (i) are not at an increased risk of bleeding from the GI or GU tract and do not have high-grade thrombocytopenia (<50 G/L) and (ii) do not currently or are not suspected in the near future to be treated with medication that strongly interact with DOAC. As an alternative, we use LMWH. However, VKA might be a reasonable alternative, if DOAC and LMWH are contraindicated or unavailable. All treatment decisions should be made in the sense of informed shared decision-making after educating the patient. Treatment should regularly be clinically monitored to optimise therapy adherence, and toevaluate issues that could affect bioavailability, for example, due to nausea and vomiting or newly administered drugs that might have a potential for drug–drug interactions. We treat patients with cancer-associated DVT and PE preferably for 6 months, and continue anticoagulation for secondary prevention of VTE, if cancer is not in complete remission and/or anti-cancer therapies are ongoing.

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ORCID iD

Cihan Ay http://orcid.org/0000-0003-2607-9717

REFERENCES

1 Horsted F, West J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. *PLoS Med* 2012;9:e1001275.
2 Heit JA. Epidemiology of venous thromboembolism. *Nat Rev Cardiol* 2015;12:464–74.
3 Cohoon KP, Ransom JE, Leibson CL, *et al*. Direct medical costs attributable to cancer-associated venous thromboembolism: a population-based longitudinal study. *Am J Med* 2016;129:1000.e15–e25.
4 Merkow RP, Bilimoria KY, Tomlinson JS, *et al*. Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. *Ann Surg* 2014;260:372–7.
5 Elting LS, Escalante CP, Cooksley C, *et al*. Outcomes and cost of deep venous thrombosis among patients with cancer. *Arch Intern Med* 2004;164:1653–61.
6 Khorana AA, Francis CW, Culakova E, *et al*. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost* 2007;5:632–4.
7 Chew HK, Wun T, Harvey D, *et al*. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Arch Intern Med* 2006;166:458–64.
8 Sørensen HT, Mellemkjaer L, Olsen JH, *et al*. Prognosis of cancers associated with venous thromboembolism. *N Engl J Med* 2000;343:1846–50.
9 Hutten BA, Prins MH, Gent M, *et al*. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. *J Clin Oncol* 2000;18:3078–83.
10 Prandoni P, Lensing AWA, Piccioli A, *et al*. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood* 2002;100:3484–8.
11 Lee AYY, Levine MN, Baker RI, *et al*. Low-Molecular-Weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003;349:146–53.
12 Schulman S, Goldhaber SZ, Kearon C, *et al*. Treatment with dabigatran or warfarin in patients with venous thromboembolism and cancer. *Thromb Haemost* 2015;114:150–7.
13 Prins MH, Lensing AWA, Brighton TA, *et al*. Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials. *Lancet Haematol* 2014;1:e37–46.
14 Agnelli G, Buller HR, Cohen A, *et al*. Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the amplify trial. *J Thromb Haemost* 2015;13:2187–91.
15 Raskob GE, van Es N, Segers A, *et al*. Edoxaban for venous thromboembolism in patients with cancer: results from a non-inferiority subgroup analysis of the Hokusai-VTE randomised, double-blind, double-dummy trial. *Lancet Haematol* 2016;3:e379–87.
16 van Es N, Coppens M, Schulman S, *et al*. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. *Blood* 2014;124:1968–75.
17 Raskob GE, van Es N, Verhamme P, *et al*. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med* 2018;378:615–24.
18 Young AM, Marshall A, Thirlwall J, *et al*. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol* 2018;36:2017–23.

19 McBane R, Wysokinski WE, Le-Rademacher JG, *et al*. Apixaban and dalteparin in active malignancy associated venous thromboembolism: the ADAM VTe trial. *J Thromb Haemost* 2019. doi:10.1111/jth.14662. [Epub ahead of print: 20 Oct 2019].
20 Agnelli G, Becattini C, Bauersachs R, *et al*. Apixaban versus dalteparin for the treatment of acute venous thromboembolism in patients with cancer: the Caravaggio study. *Thromb Haemost* 2018;118:1668–78.
21 Khorana AA, Noble S, Lee AYY, *et al*. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. *J Thromb Haemost* 2018;16:1891–4.
22 Farge D, Frere C, Connors JM, *et al*. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol* 2019;20:e566–81.
23 Key NS, Khorana AA, Kuderer NM, *et al*. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. *J Clin Oncol* 2019. doi:10.1200/JCO.19.01461. [Epub ahead of print: 5 Aug 2019].
24 Samuelson Bannow BR, Lee AYY, Khorana AA, *et al*. Management of anticoagulation for cancer-associated thrombosis in patients with thrombocytopenia: a systematic review. *Res Pract Thromb Haemost* 2018;2:664–9.
25 Samuelson Bannow BT, Lee A, Khorana AA, *et al*. Management of cancer-associated thrombosis in patients with thrombocytopenia: guidance from the SSC of the ISTH. *J Thromb Haemost* 2018;16:1246–9.
26 Gelosa P, Castiglioni L, Tenconi M, *et al*. Pharmacokinetic drug interactions of the non-vitamin K antagonist oral anticoagulants (NOACs). *Pharmacol Res* 2018;135:60–79.
27 Short NJ, Connors JM. New oral anticoagulants and the cancer patient. *Oncologist* 2014;19:82–93.
28 Riess H, Ay C, Bauersachs R, *et al*. Use of direct oral anticoagulants in patients with cancer: practical considerations for the management of patients with nausea or vomiting. *Oncologist* 2018;23:822–39.
29 Hakeam HA, Al-Sanea N. Effect of major gastrointestinal tract surgery on the absorption and efficacy of direct acting oral anticoagulants (DOACs). *J Thromb Thrombolysis* 2017;43:343–51.
30 Mani H, Kasper A, Lindhoff-Last E. Measuring the anticoagulant effects of target specific oral anticoagulants-reasons, methods and current limitations. *J Thromb Thrombolysis* 2013;36:187–94.
31 Byon W, Nepal S, Schuster AE, *et al*. Regional gastrointestinal absorption of apixaban in healthy subjects. *J Clin Pharmacol* 2018;58:965–71.
32 Parasrampuria DA, Kanamaru T, Connor A, *et al*. Evaluation of regional gastrointestinal absorption of edoxaban using the enterion capsule. *J Clin Pharmacol* 2015;55:1286–92.
33 Martin KA, Lee CR, Farrell TM, *et al*. Oral anticoagulant use after bariatric surgery: a literature review and clinical guidance. *Am J Med* 2017;130:517–24.
34 Marin-Romero S, Jara-Palomares L. Extended treatment of cancer-associated thrombosis. *Thromb Res* 2019;181:1–9.
35 Baumann Kreuziger L, Gaddh M, Onadeko O, *et al*. Wide variation in duration of anticoagulation after catheter-related thrombosis: a venous thromboembolism network US multicenter retrospective cohort study. *Blood* 2018;132:1248.
36 Zwicker JI, Connolly G, Carrier M, *et al*. Catheter-associated deep vein thrombosis of the upper extremity in cancer patients: guidance from the SSC of the ISTH. *J Thromb Haemost* 2014;12:796–800.
37 Kopolovic I, Lee AYY, Wu C. Management and outcomes of cancer-associated venous thromboembolism in patients with concomitant thrombocytopenia: a retrospective cohort study. *Ann Hematol* 2015;94:329–36.
38 Di Nisio M, Lee AYY, Carrier M, *et al*. Diagnosis and treatment of incidental venous thromboembolism in cancer patients: guidance from the SSC of the ISTH. *J Thromb Haemost* 2015;13:880–3.
39 Wu M, Schuster M, Tadros M. Update on management of portal vein thrombosis and the role of novel anticoagulants. *J Clin Transl Hepatol* 2019;7:1–11.
40 Quencer KB, Friedman T, Sheth R, *et al*. Tumor thrombus: incidence, imaging, prognosis and treatment. *Cardiovasc Diagn Ther* 2017;7:S165–77.
41 Kearon C, Akl EA, Ornelas J, *et al*. Antithrombotic therapy for VTe disease: chest guideline and expert panel report. *Chest* 2016;149:315–52.
42 Ageno W, Beyer-Westendorf J, Garcia DA, *et al*. Guidance for the management of venous thrombosis in unusual sites. *J Thromb Thrombolysis* 2016;41:129–43.
43 Meyer G, Marjanovic Z, Valcke J, *et al*. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. *Arch Intern Med* 2002;162:1729–35.
44 Deitcher SR, Kessler CM, Merli G, *et al*. Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. *Clin Appl Thromb Hemost* 2006;12:389–96.
45 Lee AYY, Kamphuisen PW, Meyer G, *et al*. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. *JAMA* 2015;314:677–86.