Treatment of Cancer-Associated Thrombosis: An Update

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Abstract

Patients with cancer are at increased risk of venous thromboembolism (VTE). Treatment of VTE remains challenging due to a significant risk of both VTE recurrence and bleeding compared with patients without underlying malignancy. Moreover, patients with cancer often present with several comorbidities such as tumor- or treatment-induced bone marrow failure, renal impairment, and extensive concomitant anticancer or supportive medication, resulting in potential drug–drug interactions. Further challenging circumstances include gastrointestinal (GI) disorders, in the context of a GI intraluminal tumor itself, GI surgery, or systemic therapy-induced GI toxicity. However, treatment options and study data in the management of cancer-associated thrombosis (CAT) have expanded over the last few years. As a result, it is becoming increasingly important to assess the patient's individual risk of bleeding and its comorbidities, and the patient's personal preferences. Prospectively, further therapeutic strategies such as factor XIa inhibitors are under clinical investigation. The aim of our narrative review is to summarize the current literature on therapy options for CAT, including common treatment situations encountered in the management of patients with cancer.

Keywords
- cancer
- thrombosis
- treatment
- anticoagulants
- bleeding

Zusammenfassung

Tumorpatienten weisen ein gesteigertes Risiko für die Entwicklung von venösen Thromboembolien (VTE) auf. Aufgrund des erhöhten Rezidiv- und Blutungsrisiko stellt die Behandlung von tumor-assoziierten Thromboembolien oft eine Herausforderung dar. Darüber hinaus haben Tumorpatienten oft relevante Begleiterkrankungen wie eine Tumor- oder Therapie-vermittelte Beeinträchtigung der Hämatopoese, eine eingeschränkte Nierenfunktion und/oder eine umfangreiche Anti-Tumor- oder Begleitmedikation, die in Arzneimittel-Wechselwirkungen resultieren kann. Ferner sind häufig gastrointestinale (GI) Störungen zu berücksichtigen, entweder durch intraluminal gelegene GI-Tumore, chirurgische abdominelle Eingriffe oder zytotoxische Effekte der Krebstherapie auf den GI-Trakt. Erfreulicherweise wurden in den letzten Jahren weitere Therapieoptionen und Studienergebnisse in der Behandlung tumor-assoziierter Thromboembolien aufgezeigt. Entsprechend sollte in der Therapieauswahl einer tumor-assoziierten VTE der Fokus verstärkt auf die Einordnung des individuellen

Schlagwörter
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Blutungsrisikos, der Komorbiditäten und der jeweiligen Patientenpräferenz liegen. Gegenwärtig werden neue Therapieansätze wie Faktor XIa-Inhibitoren in klinischen Studien getestet. Das Ziel unseres Reviews ist es, die aktuelle Literatur zu Therapieoptionen der tumorassoziierten VTE einschließlich häufig auftretender Herausforderungen in der Behandlung von Tumorpatienten zusammenzufassen und einzuordnen.

Introduction

Over the past two decades, the risk of venous thromboembolism (VTE) in patients with cancer has increased threefold, according to a large population-based cohort study with almost 500,000 patients with cancer from Denmark.[1] Not only has the outcome of patients with cancer improved with better survival rates, but the quality and frequency of imaging follow-up examinations have also increased, resulting in better detection of incidental pulmonary embolisms (PEs). In line with this, the Danish cohort study revealed that only the incidence of PE increased while the incidence of deep-vein thrombosis (DVT) remained stable over the observation time.

Furthermore, the VTE risk is distinctively high in patients receiving systemic anticancer treatment.[1–3] In this context, the impact of the emerging cancer immunotherapies on patient's VTE risk is still under discussion with a cumulative risk of VTE of up to 24% reported in real-world studies.[4,5]

Furthermore, the risk of cancer-associated thrombosis (CAT) essentially depends on the underlying tumor entity with pancreatic, ovarian, and stomach cancer at particularly high risk.[1,6]

Patients with CAT have a worse prognosis than cancer patients without thrombosis.[7,8] Not only is thromboembolism a leading cause of death in patients with cancer, but it is also likely to be an indicator of a more advanced and/or aggressive tumor disease.[9–11] Furthermore, delays in cancer treatment may occur due to the thromboembolic event.

Importantly, patients with cancer also face an increased risk of bleeding complications, even in the absence of antithrombotic medication. In a recent prospective cohort study including a total of 702 unselected patients with cancer that started systemic antitumor therapy, the 6-month cumulative incidence for clinically relevant bleeding was 8.1% (95% confidence interval [CI]: 6.1–10.3) and for major bleeding it was 4.2% (95% CI: 2.9–6.0), respectively.[12] Importantly, 38.9% were considered tumor bleeds, and only 28.2% of bleeding events occurred in patients under anticoagulation treatment. Moreover, a multicenter observational study on 199 palliative care units, which included 1,199 patients — of whom 91% were admitted due to an underlying cancer diagnosis — revealed a 3-month cumulative incidence of clinically relevant bleeding of 9.8% (95% CI: 8.3–11.6).[13] Interestingly, 44% of the patients received prophylactic and only 5.7% received therapeutic anticoagulation, respectively, and 14% were under antiplatelet therapy.

Besides the increased risk of bleeding, patients with cancer and their caregivers face further challenges with regard to anticoagulation treatment of CAT. Patients with cancer often suffer from numerous comorbidities. These include renal insufficiency, the need for extensive concomitant medication, surgical interventions, and GI symptoms such as nausea, vomiting, diarrhea, and mucositis. Additionally, these patients may suffer from thrombocytopenia due to the tumor itself or anticancer treatment.

In recent years, the treatment of CAT has evolved substantially. Results of several randomized controlled trials and real-world data have shown the benefits and risks of long-term treatment with low-molecular-weight heparin (LMWH) and direct oral anticoagulants (DOACs) in cancer patients.[14–19]

As multiple therapy options exist nowadays, the treatment decision process increasingly prioritizes the individual patient's characteristics, including their VTE recurrence and bleeding risks.

This narrative review, using an illustrative case report, aims to provide an overview of the current state of research on the treatment of VTE in patients with cancer. The goal of our review is to assist clinicians in applying the latest study results to individual patient care at the bedside.

Case Report

A 67-year-old female patient was admitted to the emergency room with dyspnea and hemoptysis. Moreover, she suffered from weight loss and increasing retrosternal discomfort when swallowing. The patient had a history of early breast cancer 12 years ago, and XXX of DVT of the left leg while receiving tamoxifen. The patient was hemodynamically stable. Laboratory examination revealed low hemoglobin (10.5 g/dL) and an elevated d-dimer (5.5 mg/L). As PE was suspected, a chest computed tomography (CT) angiography was performed and a PE was detected in the left pulmonary artery (►**Fig. 1**). In further diagnostic workup, including upper GI endoscopy, biopsy of circumferential masses of the lower esophagus, and whole-body integrated fluorodeoxyglucose (FDG) positron emission tomography-CT scan, a locally advanced esophageal adenocarcinoma with regional and distant lymph node and liver metastases was diagnosed. In the biomarker assessment, the tumor was positive for programmed cell death-ligand 1 (PD-L1) expression (CPS 5%), and negative for human epidermal growth factor receptor 2 (Her2). Hence, the patient was offered systemic palliative chemotherapy including oxaliplatin, fluorouracil, and leucovorin combined with immunotherapy with nivolumab. During the inpatient hospitalization, the patient received anticoagulant treatment with LMWH.

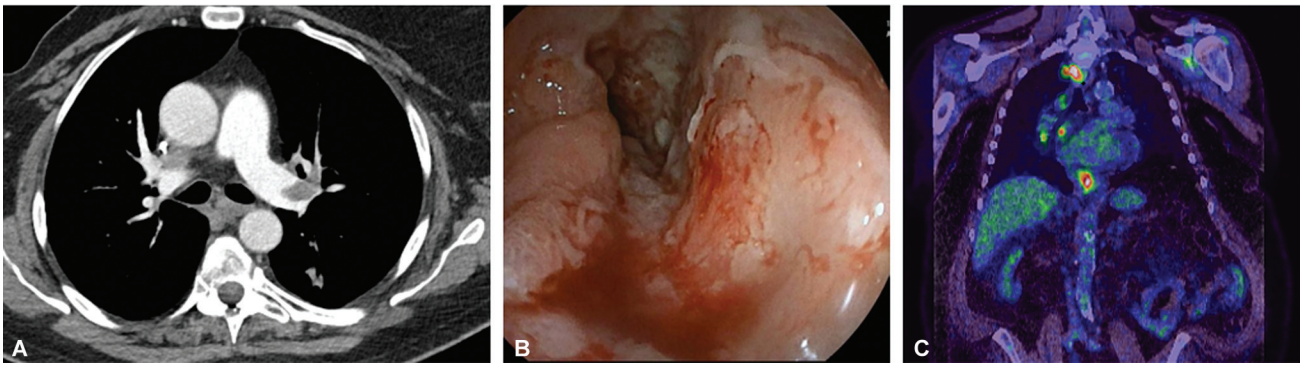

Fig. 1 (**A**) Computed tomography pulmonary angiography showed embolism of the left pulmonary artery. (**B**) Esophagogastroduodenoscopy revealed a circumferential mass of the lower esophagus. (**C**) Together with histological confirmation, a locally advanced esophageal adenocarcinoma with regional and distant lymph node and liver metastases, as shown by a whole-body integrated fluorodeoxyglucose positron emission tomography-CT scan was diagnosed. (© University Hospital Regensburg.)

When the patient is discharged, the question arises whether to switch the anticoagulant therapy to a DOAC.

Anticoagulation Regimen

In the past, patients with CAT treated with vitamin K-antagonists (VKA) after initial heparin treatment have shown unsatisfactory high incidences of VTE recurrence as well as bleeding.[20] VKAs are characterized by slow onset and offset, drug and food interactions, as well as the need for routine laboratory monitoring, resulting in frequent periods out of therapeutic range.

Based on these observations, multiple randomized controlled trials have been conducted assessing anticoagulation with LMWH-bridged VKA compared with long-term anticoagulation with LMWH in patients with cancer. In the CLOT trial, dalteparin 200 IU/kg body weight once daily (OD) for 1 month followed by 150 IU/kg body weight OD for further 5 months was compared with VKA.[19] A total of 672 patients with active cancer and acute symptomatic proximal DVT and/or PE were included. In the dalteparin arm, the risk of recurrent VTE was significantly reduced compared with treatment with VKA (8 vs. 16%, hazard ratio [HR]: 0.48; 95% CI: 0.30–0.77). With regard to bleeding, the safety of anticoagulation was similar between dalteparin and VKA. In the more recent CATCH trial, 900 patients with active cancer and acute symptomatic proximal DVT and/or PE were randomly assigned to tinzaparin 175 IU/kg body weight OD for 6 months or LMHW-bridged VKA.[18] Compared with VKA, treatment with tinzaparin resulted in a nonsignificant risk reduction of recurrent VTE as the primary outcome with an HR of 0.65 (95% CI: 0.41–1.03). While major bleeding was similar between both treatment arms, clinically relevant nonmajor bleeding (CRNMB) occurred significantly less often in the tinzaparin arm (11 vs. 15%, HR: 0.58; 95% CI: 0.49–0.84). In a network meta-analysis including further smaller trials, long-term treatment (3–6 months) with LMWH appeared to be significantly superior to VKA with regard to risk reduction of VTE recurrence (RR: 0.60; 95% CI: 0.45–0.79), and was similarly safe compared with VKA therapy.[21–23]

As a result, international guidelines recommended LWMH as the anticoagulant of choice for treatment and secondary prevention of CAT.[24]

However, long-term use of LMWH is associated with a high burden due to its need for daily subcutaneous injections and treatment costs.[25] Real-world data from the year 2016 have shown that a relevant proportion of patients with CAT still received treatment with VKA.[26,27] Therefore, the introduction of DOACs for the treatment of VTE in the general patient population has evoked strong interest in exploring their specific use in cancer patients. In all pivotal phase 3 studies of DOACs for the treatment of VTE, only a minority of participants had a history of cancer, active cancer, or were diagnosed with cancer during the treatment phase.[28–30] Furthermore, patients in the control arm were treated with LWMH-bridged VKA, but not with long-term application of LMWH. However, an indirect comparison of LMWH versus DOACs within a network meta-analysis, including patients with cancer only, was subsequently published.[23] Here, DOACs were suggested to be comparably effective (RR = 1.08; 95% CI: 0.59–1.95), and — numerically only — safer than LMWH in the treatment of CAT (RR: 0.67, 95% CI: 0.31–1.46).

Consequently, randomized controlled trials followed, including patients with active cancer only, evaluating the respective direct factor Xa inhibitor (edoxaban, rivaroxaban, or apixaban) in comparison to LMWH as the standard treatment.[14,15,17]

In 2018, results of the HOKUSAI VTE cancer study, a noninferior randomized controlled trial, assessing edoxaban versus LMWH in patients with active cancer and either symptomatic or incidental DVT and/or PE were published.[14] A total of 1,050 patients were randomly assigned to either LWMH for at least 5 days followed by edoxaban 1 × 60 mg OD for 6 to 12 months, or dalteparin according to the regimen used in the CLOT trial. With regard to the composite primary endpoint (VTE recurrence or major bleeding during the first 12 months), edoxaban was shown to be noninferior to dalteparin (12.8 vs. 13.5%, HR: 0.97; 95% CI: 0.70–1.36, $p = 0.006$). Following the secondary outcome, patients treated with edoxaban experienced fewer recurrent VTE events, particularly DVT, compared with those treated with dalteparin, though the difference was not statistically significant (7.9 vs. 11.3%, HR: 0.71; 95% CI: 0.48–1.06). The

risk of major bleeding was statistically higher among patients in the edoxaban arm versus dalteparin (6.9 vs. 4.0%, HR: 1.77; 95% CI: 1.03–3.04), while CRNMB was similar between both patient groups (14.6 vs. 11.1%, HR: 1.38; 95% CI: 0.98–1.94). Importantly, the higher incidence of major bleeding within the edoxaban group was confined to patients with GI cancer and particularly occurred as (predominantly upper) GI bleeding complications.[31]

In the same year, results of the randomized pilot trial SELECT-D were available.[15] A total of 406 patients with active cancer and either symptomatic or incidental PE and/or symptomatic proximal DVT were included and randomized to rivaroxaban 15 mg twice daily (BID) for 3 weeks, followed by 20 mg OD for a total of 6 months, or dalteparin according to the CLOT regimen. Notably, following an interim safety analysis of the first 220 randomized patients, showing a nonsignificant higher incidence of major bleeding in patients with cancer of the esophagus or gastroesophageal junction in the rivaroxaban arm, those patients were no longer included in the study. In the final analysis, a total of 30 patients with this entity (7.4%), and 11 (2.7%) further patients with gastric cancer were observed. In the rivaroxaban group, the 6-month cumulative VTE recurrence rate was significantly reduced to 4% compared with 11% among patients treated with dalteparin (HR: 0.43; 95% CI: 0.19–0.99). While there was no significant difference in major bleeding (6% for rivaroxaban vs. 4% for dalteparin; HR: 1.83; 95% CI: 0.68–4.96), CRNMB occurred significantly more often among patients receiving rivaroxaban than dalteparin (13 vs. 4%, HR: 3.76; 95% CI: 1.63–8.69). Most major bleeding and CRNMB events were of GI — and for CRNMB additionally urogenital — origin. Major bleeds occurred in 36% (4/11) of patients with cancer of the esophagus or gastroesophageal junction treated with rivaroxaban, and in 5% (1/19) of patients treated with dalteparin.

Two years later, the final results of the CARAVAGGIO study, a randomized noninferiority trial evaluating apixaban in the treatment setting of CAT followed.[17] A total of 1,155 patients with active cancer were randomized to apixaban 10 mg BID for 7 days, followed by 5 mg BID for 6 months or dalteparin according to the CLOT protocol. With regard to the primary outcome of the study, apixaban demonstrated noninferiority in the prevention of recurrent VTE during the treatment period compared with dalteparin (5.6 vs. 7.9%, HR: 0.63; 95% CI: 0.37–1.07, $p < 0.001$ for noninferiority). Major bleeding, as the principal safety outcome, did not differ between both treatment arms (apixaban: 3.8% vs. dalteparin: 4.0%, HR: 0.82; 95% CI: 0.40–1.69). Notably, major GI bleeding events occurred with equal frequency in patients treated with apixaban (1.9%) and dalteparin (1.7%, HR: 1.05; 95% CI: 0.44–2.50). CRNMB were numerically higher in the apixaban arm (9.0 vs. 6.0%, HR: 1,42; 95% CI: 0.88–2.30), mainly due to bleeding events in the genitourinary (GU) and upper airway tract.[32]

Considering all three studies together, they are all comparable with regard to the study protocols and patient cohorts. However, several discrepancies including exclusion criteria, outcome parameters, and patient characteristics have to be considered when interpreting the results (►Table 1).

In a recent meta-analysis including a total of 3,690 patients of the above-mentioned studies as well as of three smaller randomized trials (ADAM-VTE on apixaban, CASTA-DIVA on rivaroxaban, and CANVAS on any of the DOACs apixaban, dabigatran, edoxaban, or rivaroxaban), a significant risk reduction of VTE recurrence was demonstrated with DOACs in comparison to LMWH (RR: 0.67; 95% CI: 0.52–0.85).[33] In the LMWH patient cohort, the absolute VTE recurrence rate was 8.3%, whereas the absolute risk reduction in the DOACs patient cohort was 2.7% (95% CI: −4 to −1.2). With regard to safety, there was a numerically, but not significantly, higher rate of major bleeding in the DOAC patient cohort compared with LMWH (4.3 vs. 3.7%, RR: 1.17; 95% CI: 0.82–1.67). However, CRNBM occurred significantly more frequently in patients treated with DOACs compared with those receiving LMWH (RR: 1.66; 95% CI: 1.31–2.09). The risk of CRNMB was 5.7% in patients receiving LMWH, whereas the absolute risk increase with DOACs was 3.8% (95% CI: 1.8–6.2). All-cause mortality did not significantly differ in any of the included studies between patients treated with DOACs and those with LMWH (23.3 vs. 23.5%, RR: 1.02; 95% CI: 0.89–1.16).

Drug–Drug Interactions

While LMWH is considered pharmacologically inert, potential drug interactions have to be kept in mind when treating patients with DOACs. Edoxaban, rivaroxaban, and apixaban are substrate of P-glycoprotein.[34] Furthermore, they are all metabolized by CYP3A4, although to a different extent (edoxaban <4%, rivaroxaban 18%, and apixaban 25%, respectively). Concurrent medication with strong inhibitors or inductors of P-glycoprotein and CYP3A4, respectively, is not recommended in patients with VTE treated with DOACs. However, most data on drug interactions are based on preclinical data and pharmacokinetic studies with healthy volunteers only, and most of the trials assessing DOACs in the treatment of VTE excluded patients with medication potentially causing relevant pharmacokinetic interactions.[35–37] Interestingly, a post hoc analysis of the CARAVAGGIO study with respect to concomitant anticancer treatment demonstrated that there was no significant difference, neither in efficacy nor in safety, between patients receiving concomitant antitumor agents and those who did not in both, in the apixaban and dalteparin arm, respectively.[38] However, it should be taken into account that some subgroups were relatively small.

Guideline Recommendations

Based on these data, current guidelines consider both LMWH and DOACs as preferred treatment options in the acute and long-term treatment of CAT (►Table 2).[39–42] Nonetheless, a personalized treatment approach is essential, particularly when considering the patient's individual bleeding risk profile.

In patients with a high risk of GI or GU bleeding, either in patients with luminal GI or urogenital tumors — particularly if unresected — and/or in patients with an increased risk of GI toxicity (e.g., mucositis), treatment with LMWH should be

Table 1 Current guideline recommendations in the treatment of cancer-associated thrombosis

	ASCO 2023[39]	ESMO 2023[41]	AWMF 2023[40]	ITAC 2022[42]
Initial treatment[a,b]	LMWH,[c] UFH, fondaparinux, rivaroxaban, or apixaban	LMWH,[c] UFH, fondaparinux,[d] apixaban, or rivaroxaban	LMWH, apixaban, edoxaban, or rivaroxaban	LMWH,[c] UFH, fondaparinux, or—in patients without high risk of GI or GU bleeding—rivaroxaban, apixaban, or edoxaban[e]
Long-term treatment†	LMWH, apixaban, edoxaban, or rivaroxaban, or VKA[g]	LMWH, apixaban, edoxaban, rivaroxaban, or VKA (>6 mo of treatment)	LMWH, apixaban, edoxaban, or rivaroxaban	LMWH or—in patients without strong drug–drug interactions or GI absorption impairment—rivaroxaban, apixaban, or edoxaban
Caution with DOACs	• GI or GU tumors • Otherwise high risk for mucosal bleeding • Drug–drug interactions	• Luminal GI cancer • Strong drug–drug interactions	• Luminal cancer • High risk of bleeding (thrombocytopenia) • Relevant drug–drug interactions • GI absorption impairment	• GI tumors, particularly upper GI tract tumors
Remark		LMWH is recommended in patients with brain metastases		
Duration of treatment	≥ 6 mo	≥ 6 mo	≥ 3–6 mo	≥ 6 mo

Abbreviations: ASCO, American Society of Clinical Oncology; AWMF, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften; CAT, cancer-associated thrombosis; CrCl, creatinine clearance; DOAC, direct oral anticoagulants; ESMO, European Society of Medical Oncology; GI, gastrointestinal; GU, genitourinary; HIT, heparin-induced thrombocytopenia; ITAC, International Initiative on Thrombosis and Cancer; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonist.
[a]Distinct definitions of initial treatment must be considered. ASCO and AWMF: no further specification. ESMO: 5–10 days. ITAC: up to 10 days.
[b]Edoxaban started after ≥ 5 days of parenteral anticoagulation.
[c]LMWH is preferred over UFH in patients with CrCl ≥ 30 mL/min.
[d]Fondaparinux in patients with a history of type 2 HIT.
[e]LMWH or DOAC, or both, only in patients with CrCl ≥ 30 mL/min.
[f]Distinct definitions of long-term treatment have to be considered. ASCO and AWMF: no further specification. ESMO: 3–6 months and >6 months (extended). ITAC: up to 6 months (early) and beyond 6 months (long-term).
[g]VKA if LMWH or DOACs are not accessible.

preferred. Furthermore, patients with expected strong drug–drug interactions should be consulted for parenteral anticoagulation with LMWH. The preferred anticoagulation regimen may change over the course of the disease, and, due to comparable half-life periods, switching from DOACs to LMWH and vice versa can easily and safely be performed.

In the initial treatment phase (i.e., 5–10 days), unfractionated heparin (UFH) and fondaparinux are often mentioned as additional options. However, UFH should only be considered in patients with severe renal impairment (creatinine clearance [CrCl] <30 mL/min), and fondaparinux in case of previous type 2 heparin-induced thrombocytopenia (HIT) or in patients allergic to heparin.[39,41]

Further Considerations

Renal Impairment

Patients with cancer often show impaired renal function. In a French multicenter observational study of nearly 5,000 patients with cancer, almost 20% of patients showed a reduced CrCl of less than 59 mL/min.[43] Renal impairment (RI) is associated with an increased risk of both thrombosis and bleeding.[44] Moreover, accumulation of anticoagulants may occur with impaired renal clearance, further increasing the bleeding risk. LMWHs undergo primarily renal elimination. However, the renal elimination of LMWHs depends on the molecular weight of each LMWH. Agents with higher mean molecular weights are less renally cleared (e.g., dalteparin or tinzaparin) compared with those with lower molecular weights (e.g., enoxaparin or nadroparin).[45] In the CLOT trial, patients with serum creatinine level >3 × the upper normal limit were excluded. As a result, 162 of 676 included patients (24%) showed moderate to severe RI (CrCl <60 mL/min). A post hoc analysis of these patients revealed that, in comparison to patients without RI, patients with a CrCl <60 mL/min showed increased bleeding events in both treatment arms, VKA and dalteparin (within the dalteparin arm, 20.3% in

Table 2 Study design and patient characteristics of the large, randomized trials assessing oral direct FXa inhibitors in the treatment of CAT

	HOKUSAI VTE cancer[14]	SELECT-D[15]	CARAVAGGIO[17]
Study design			
Planned enrollment (no. of patients)	1,000	530	1,168
Treatment			
DOAC	Edoxaban 60 mg OD (after ≥5 d of LMWH)	Rivaroxaban 15 mg BID for 21 d, followed by 20 mg OD	Apixaban 10 mg BID for 7 d, followed by 5 mg BID
LMWH	Dalteparin 200 IU/kg OD for 1 mo, followed by 150 IU/kg OD		
Treatment duration	6–12 mo	6 mo	6 mo
Inclusion criteria			
VTE diagnosis	Symptomatic or incidental proximal DVT and/or PE (segmental or more proximal if incidental)	Symptomatic proximal DVT and/or symptomatic or incidental PE	Symptomatic or incidental proximal DVT and/or PE (segmental or more proximal if incidental)
Cancer	Cancer diagnosed within the past 2 y or active cancer (cancer diagnosed and/or treated within the past 6 mo or at the time of enrollment; recurrent, regionally advanced, or metastatic cancer; hematologic cancer without CR)	Cancer diagnosed within the past 2 y or active cancer (cancer diagnosed and/or treated within the past 6 mo or at the time of enrollment; recurrent, regionally advanced, or metastatic cancer; hematologic cancer without CR)	Cancer diagnosed within the past 2 y or active cancer (diagnosed and/or treated within the past 6 mo or at the time of enrollment; recurrent, regionally advanced, or metastatic)
Excluded cancer entities	Basal-cell or squamous-cell skin cancer	Basal-cell or squamous-cell skin cancer; after safety analysis of the first 220 patients, patients with cancer of the esophagus or gastroesophageal junction were subsequently excluded	Basal-cell or squamous-cell skin cancer, primary brain tumor, known intracerebral metastases, acute leukemia
Outcome parameters			
Primary outcome	Composite of recurrent VTE or major bleeding	Recurrent VTE	Recurrent VTE
Secondary outcome	Recurrent VTE, major bleeding, CRNMB (among others)	Major bleeding, CRNMB	Major bleeding, CRNMB, recurrent VTE, or major bleeding (among others)
Patient characteristics			
Number of patients included	1,050	406	1,170
Number of patients included in the intention-to-treat analysis	1,046	406	1,155
Age, means ± SD and median (range), respectively	64.3 ± 11 (edoxaban), 63.7 ± 11.7 (dalteparin)	67 (22–87; rivaroxaban), 67 (34–87; dalteparin)	67.2 ± 11.3 (apixaban), 67.2 ± 10.9 (dalteparin)
Active cancer, no. (%)	1,024 (97.9)	406 (100)	1,124 (97.3)
Metastatic disease, no. (%)	554 (53)	236 (58.1)	785 (68)[a]

Table 2 (*Continued*)

	HOKUSAI VTE cancer[14]	SELECT-D[15]	CARAVAGGIO[17]
Currently cancer treatment, no. (%)	757 (72.4)[b]	282 (69.5)	717 (62.1)
Patients with upper GI cancer, no. (%)	54 (5.2)	41 (10.1)	54 (4.7)
Qualifying VTE			
PE with or without DVT, no. (%)	657 (62.8)	82 (20.2)[c]	638 (55.2)
Incidental VTE, no. (%)	340 (32.5)[d]	213 (52.5)[e]	230 (19.9)[d]
Median treatment duration (months)	Edoxaban: 6.9 Dalteparin: 6.0	Rivaroxaban: 5.8 Dalteparin: 5.9	Apixaban: 5.9 Dalteparin: 5.8

Abbreviations: BID, twice daily; CAT, cancer-associated thrombosis; CR, complete response; CRNMB, clinically relevant nonmajor bleeding; DOAC, direct oral anticoagulant; DVT, deep-vein thrombosis; GI, gastrointestinal; LMWH, low-molecular-weight heparin; OD, once daily; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.
[a]Including recurrent locally advanced cancer.
[b]Cancer treatment within the previous 4 weeks.
[c]Only symptomatic VTE is included.
[d]DVT and PE included.
[e]Only patients with PE were included (six patients with PE had additional DVT).

patients with RI vs. 11.8% without RI).[46] Comparing the anticoagulation regimen in patients with RI only, the VTE recurrence rate was significantly lower in the dalteparin arm compared with VKA (2.7 vs. 17%, HR = 0.15; 95% CI: 0.03–0.65), while the bleeding risk was similar between both treatment groups. In the CATCH trial, 131 of 864 included patients (15%) showed RI at baseline (CrCl <60 mL/min). While no significant difference in VTE recurrence or bleeding was observed between tinzaparin and VKA in patients with RI, RI was associated with a significant increase in VTE recurrence (RR: 1.74; 95% CI: 1.06–2.85) and major bleeding risk (RR: 2.98; 95% CI: 1.29–6.90) compared with the study population without kidney disease in both treatment arms.[47]

In all large randomized controlled trials of DOACs in patients with CAT, patients with severe RI, defined as CrCl <30 mL/min, were excluded.[14,15,17] Therefore, subgroup analyses are available only for patients with moderate renal impairment. In the CARAVAGGIO trial, 275 of 1,142 patients (24%) suffered from RI with a CrCl of 30 to 59 mL/min. In a prespecified analysis, moderate RI was neither associated with a higher risk for VTE recurrence nor major bleeding compared with patients without RI.[48] Within the cohort of patients with RI, apixaban significantly reduced VTE recurrence in comparison to dalteparin (HR: 0.27; 95% CI: 0.08–0.96). Recently, results of a subgroup analysis of the ONCO DVT study, evaluating a 3- versus 12-month treatment regimen with edoxaban in cancer patients with isolated distal DVT were published.[49] 21.8% of patients (131/601) had a CrCl <50 mL/min. First, a 12-month regimen was superior in preventing VTE recurrence compared with 3 months of treatment, irrespective of renal function. Second, patients with RI did not suffer from an increase in bleeding within 12 months of treatment compared with 3 months only.

Gastrointestinal Drug Absorption

Cancer patients may suffer from treatment-induced mucositis, resulting in impaired oral food intake. Noteworthy, rivaroxaban requires food intake to elevate its bioavailability, with an increase of the area under the curve (AUC) and peak concentration of a 20-mg tablet by 39 and 76%, respectively, when taken together with food.[50] In contrast, the bioavailability of apixaban and edoxaban, respectively, does not significantly depend on food intake.[51]

Furthermore, patients with upper GI cancers may present with anatomical changes due to surgical interventions that can alter the drug's adsorption. While apixaban and edoxaban are mainly absorbed in the proximal small intestine, rivaroxaban is primarily absorbed in the stomach.[51]

Clinical data on the use of DOACs after cancer surgery of the upper GI tract are scarce. In a single-center retrospective study of a total of 11 patients with partial or total gastrectomy due to upper GI cancer and treatment with a DOAC for VTE or atrial fibrillation, plasma concentrations of the direct FXa inhibitors rivaroxaban, apixaban, and edoxaban were shown to be within the expected range, indicating sufficient drug adsorption.[52]

Quality of Life

In the HOKUSAI VTE cancer study, the median treatment duration with edoxaban was 211 days (interquartile range [IQR], 76–357) and 184 days with dalteparin (IQR, 85–341, $p = 0.01$).[14] In the edoxaban arm, 4.9% of patients discontinued study drug treatment permanently because of the inconvenience of dosing, while it was 14.9% in the dalteparin arm. In the CARAVAGGIO and SELECT-D trials, the median duration of treatment did not differ significantly between LMWH and apixaban and rivaroxaban, respectively.[15,17] However, in the ADAM-VTE trial, a randomized safety trial of apixaban versus dalteparin in the treatment of CAT with the primary outcome of major bleeding, 6 of 145 (4.1%) patients refused further treatment with apixaban within the assigned 6-month treatment phase, while it was 22 of 142 (15.5%) patients in the dalteparin group ($p < 0.01$).[53] Moreover, in the ADAM-VTE trial, the impact of the anticoagulant treatment on quality of life was assessed by monthly anticoagulation satisfaction and bruise surveys. Treatment with dalteparin was favored only at month 1 in the measurement of confidence that the anticoagulant treatment would protect the patient from VTE recurrence. However, the overall burden and negative impact on quality of life were significantly lower in the patient cohort treated with apixaban.

Case Report (Continued)

With locally advanced esophageal cancer without prior resection, our patient has a high risk of spontaneous intraluminal GI bleeding. Furthermore, at the time of diagnosis, she complained about difficulties with swallowing, restricting her nutrition intake to a liquid diet only. When the patient was discharged after having received the first course of palliative chemoimmunotherapy, we therefore carefully discussed with the patient to continue the VTE treatment with LMWH (e.g., tinzaparin 175 IU/kg OD). After six cycles of further ambulatory treatment, the patient's symptoms declined, and a CT scan showed stable disease. Moreover, the patient increasingly felt discomfort with daily subcutaneous application of LMWH. Consequently, following a detailed discussion about treatment alternatives, anticoagulation therapy was changed from tinzaparin to apixaban (5 mg BID).

Treatment Duration

There are no randomized trials specifically addressing the optimal treatment duration in CAT. Hence, the ideal duration of anticoagulation in these patients remains uncertain. However, treatment was given for at least 6 months not only within the CLOT and CATCH trials, evaluating long-term treatment with LMWH versus VKA, but also within the DOAC trials (CARAVAGGIO, HOKUSAI-VTE cancer, and SELECT-D; ►Table 2).[14,15,17–19] Interestingly, in the SELECT-D trial, after 6 months of anticoagulation, patients with active cancer and index PE or residual DVT were eligible for further randomization to either rivaroxaban for another 6 months of treatment or placebo.[54] Due to low recruitment, the second randomization closed prematurely after 92 patients were included. The cumulative VTE recurrence rate after 6 months of treatment continuation with rivaroxaban was 4% compared with 14% in the placebo arm. However, statistical significance was not reached (HR: 0.32; 95% CI: 0.06–1.58), likely due to the small sample size. While the major and clinically relevant nonmajor bleeding rate was 0% in the placebo arm, 5 and 4% of patients, respectively, suffered from bleeding events while receiving rivaroxaban from months 6 to 12.

Furthermore, two prospective smaller studies evaluated the safety of LMWH beyond the first 6 months of anticoagulation treatment.[55,56] In the DALTECAN study, the risk of major bleeding was highest within the first month of treatment with dalteparin according to the CLOT protocol (3.6% per patient-month with dalteparin 200 IU/kg OD), while it remained low during months 2 to 6 and 7 to 12 (1.1 and 0.7% per patient-month, respectively, with dalteparin 150 IU/kg OD).[55] The VTE recurrence rate remained high from months 2 to 6 to 7 to 12 (3.4 and 4.1%, respectively). In the single-arm TiCAT study, treatment with tinzaparin 1×175 IU/kg for up to 12 months was safe with a major bleeding rate of 0.5% per patient per month during months 1 to 6 as well as months 7 to 12.[56] Most VTE recurrence events occurred during the first 6 months of treatment (4.5%; 95% CI: 2.2–7.8% vs. 1.1% in months 7–12 [95% CI: 0.1–3.9%]).

In a recent meta-analysis evaluating the efficacy and safety of extended anticoagulation beyond 6 months of treatment of VTE including treatment with LMWH and DOACs, the major bleeding rate was less frequently observed in the extended phase (1–4%) than in the first 6 months (up to 9%).[57]

Accordingly, anticoagulation in patients with CAT should be applied for at least 6 months. Patients with active cancer, particularly patients still receiving anticancer treatment, should continue anticoagulation in the absence of a high bleeding risk.[39–42] However, the risk–benefit profile might change over the course of the disease and therefore must be reevaluated at regular intervals.

Dose Reduction in Secondary Prevention

In patients without underlying cancer, VTE secondary prevention (i.e., anticoagulation beyond 6 months) with either rivaroxaban or apixaban is recommended to be continued with a reduced dose (10 mg OD or 2.5 mg BID, respectively).[40] The recently published randomized, double-blind EVE trial assessed whether this dose reduction is feasible in patients with cancer too.[58] Patients with CAT were randomly assigned to apixaban 2.5 mg BID or 5 mg BID for 12 months after having completed 6 to 12 months of previous anticoagulation treatment. There was neither a significant difference in the composite of major bleeding and CRNMB as the primary outcome (8.9% in the arm with the reduced dose of apixaban vs. 12.2% in the arm with apixaban 5 mg BID, HR: 0.72; 95% CI: 0.38–1.37) nor in the rate of recurrent VTE or ATE as secondary endpoint (each 5%, HR: 1.0; 95% CI: 0.40–2.53). The large API-CT trial (>1.700 patients planned to be included) will further

evaluate whether a reduced-dose regimen of apixaban as extended secondary prevention of VTE is effective and safe in patients with active cancer.[59]

Case Report (Continued)

Six months after initiating first-line chemoimmunotherapy, a CT scan showed continual stable disease. The patient was in good general condition, and the systemic anticancer treatment was proceeded. Anticoagulation with apixaban 5 mg BID was well tolerated. In particular, there were no signs of bleeding events. We, therefore, discussed with the patient to continue anticoagulation with apixaban without dose reduction.

Perspectives

As outlined earlier, patients receiving anticoagulation treatment of CAT are still prone to bleeding complications. Recently, factor XIa inhibitors, either small molecules, antisense oligonucleotides, or antibodies, have been developed. Since it is assumed that factor XIa inhibition might essentially impair pathologic thrombus formation, but without the relevant restriction of the physiological hemostasis, particular interest lies in its investigation in patients with VTE and cancer.[60] Currently, several randomized trials assessing FXIa inhibitors in this vulnerable patient cohort are actively recruiting (e.g., NCT05171049, NCT05171075).

Authors' Contributions

M.V. and C.H. wrote the manuscript draft. All authors contributed to the manuscript drafting, reviewed, and approved the final version.

Conflict of Interest

The authors declare that they have no conflict of interest.

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