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PALLIATIVE MEDICINE (A JATOI, SECTION EDITOR)

Anticoagulation in Cancer Patients: a Summary of Pitfalls to Avoid

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Abstract

Purpose of Review Venous thromboembolism (VTE) is a leading cause of morbidity and mortality in cancer patients, and its management is often associated with complications including risk of recurrent VTE and bleeding. Here, we review the current data on pitfalls during anticoagulation in cancer patients and measures necessary to avoid them.

Recent Findings Although low-molecular-weight heparin monotherapy has been the standard of treatment for several years, emerging data for direct oral anticoagulants (DOACs) are leading to new paradigms in treatment. Reports of recent randomized trials suggest a lower risk of recurrent thrombosis but higher risk of bleeding, particularly in gastrointestinal cancer patients, with DOACs. Careful patient selection and individualization of therapy based on risk of bleeding as well as recurrent VTE are keys.

Summary Problems like bleeding, recurrence, thrombocytopenia, drug-drug interactions, renal impairment, nausea-vomiting along with concerns about adherence arise during anticoagulation in cancer patients. However, with adequate pre-treatment assessment, correct anticoagulant selection and proper monitoring during anticoagulation, these issues can be addressed safely and effectively.

Keywords Cancer · VTE · Thromboembolism · Anticoagulation · Thromboprophylaxis · Pitfalls · Bleeding · Thrombocytopenia · Chemotherapy · LMWH · VKA · DOAC · Adherence · Renal insufficiency · Drug-drug interactions

Introduction

Venous thromboembolism (VTE) is a highly prevalent complication of cancer. VTE occurrence has been increasing in cancer patients. In a recent UK analysis evaluating cancer versus matched non-cancer controls from the general population, the hazard ratio of VTE was 4.7 (95% CI 4.5–4.9), and the incidence rate was 13.9/1000 PY (95% CI 13.4–14.4) [1]. The increased incidence may be explained partly by the increased awareness of the association of cancer with VTE, treatment advances and partly by thrombogenicity of current systemic therapy, increased use of indwelling central venous catheter, and supportive care including blood transfusions and growth factors.

VTE is associated with significant morbidity and mortality [2–4] and is one of the leading causes of death in cancer patients [4]. In cancer patients, it is also associated with increased economic burden ranging from 40 to 50% more than that in cancer patients without VTE [5, 6]. Other notable consequences of VTE in cancer include the burden of long-term anticoagulation, delays in treatment, and increased risks of bleeding as well as VTE recurrence [7]. Until recently, most guidelines including those from American Society of Clinical Oncology, European Society for Medical Oncology, and National Comprehensive Cancer Network recommended monotherapy with low-molecular-weight heparin (LMWH) for 3–6 months [8–13]. However, direct oral anticoagulants (DOACs) are emerging as an efficacious alternative [14]. Recent guidelines by the International Society on Thrombosis and Hemostasis [15•] suggest using specific DOACs (rivaroxaban or edoxaban) for acute cancer-associated VTE with low bleeding risk and no drug-drug interactions with current systemic therapy but preferring LMWH for patients with high risk of bleeding. The key to prevention and treatment of cancer-associated VTE is adequate anticoagulation with a careful and individualized approach.

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Despite the need for therapeutic anticoagulation, it is important for clinicians to be aware that this is indeed associated with substantial potential for complications in cancer patients compared to non-cancer patients. These include increased risk of bleeding compared to non-cancer patients; concomitant or intermittent thrombocytopenia; extremes of body weight; renal impairment; risk of intracranial bleeding, particularly in patients with central nervous system involvement; drug-drug interactions with systemic antineoplastic therapy; risk of PE and DVT recurrence; and agent-specific complications. Here, we review literature for potentially avoidable pitfalls during anticoagulation with current therapeutic agents in cancer patients and discuss ways to anticipate and manage these pitfalls.

Bleeding

Bleeding risk in cancer patients can be multifactorial, and those receiving anticoagulation present a special challenge in management when they present with bleeding events. Risk of bleeding in such patients is higher than those on anticoagulation without cancer. A dearth of data regarding clinical predictors of bleeding risk as well as absence of a proven predictive risk score has been an issue [16]. But there is no question that bleeding is as, if not more prevalent, than thromboembolism in the cancer population. For instance, cumulative incidence of major bleeding events from observed data in a claims database was reported to be 5.9% and 8.7% at 3 and 6 months of anticoagulation in cancer patients, respectively, compared to 2.6% and 4.2% in non-anticoagulated cancer patients [17]. Similarly, in a secondary analysis from the CATCH study of tinzaparin treatment of cancer-associated VTE, data on 900 patients treated with either LMWH or VKA in a follow-up period of 6 months showed a 15.3% incidence of clinically relevant bleeding (CRB) which included major and clinically relevant non-major bleeding events. It also showed associated confounders in age > 75 years and intracranial malignancy (primary or secondary) [18]. Here, we discuss bleeding risk by class of anticoagulant.

LMWHs A recent observational cohort study from the RIETE database showed 11.3/100 patient-years incidence of major bleeding events in a 180-day follow-up of cancer patients taking LMWH [19]. Furthermore, a cumulative incidence of 8.3% (95% CI 5.4–11) was obtained in a recent prospective cohort study leading to discontinuation of LMWH injections in 1.1% participants [20]. One area of concern is patients with intracranial malignancies. Mantia et al. reported that LMWH therapy in patients with glioma was associated with a threefold increase in incidence of major intracranial hemorrhage compared to those not anticoagulated [21].

LMWHs vs VKAs There is a significant reduction in clinically relevant non-major bleeding (CRNMB) events by tinzaparin compared to warfarin but no differences in major bleeding events in one large randomized trial [22]. A network meta-analysis by Posch et al. showed that safety of LMWH was comparable with VKAs in terms of bleeding risk [14].

LMWHs vs DOACs Two recent randomized trials have reported on the efficacy and safety of DOACs versus LMWHs. In the SELECT-D trial, there was a higher risk of major bleeding and a significant increase in the risk of CRNMB with rivaroxaban compared to dalteparin (6% vs 4% and 13% vs 4%, respectively) [23]. These results were consistent with that of the HOKUSAI trial where similar comparisons between edoxaban and dalteparin showed risk of 6.9% vs 4% for major bleeding [24•]. In a retrospective analysis by Ross et al., the rate of CRB at 6 and 9 months for LMWH is 15.4% and 17.9%, respectively, and the same for DOAC is 16.7% and 20%, respectively [25].

Recommendations

Before beginning anticoagulation, an individualized assessment of every patient's bleeding risk should be performed and high-risk patients should be identified. Factors including age, platelet count, renal and liver status, invasive diagnostic/surgical procedures, recent immobility, recent bleeding, the cancer type and intracranial malignancy, metastasis, and active chemotherapy should be taken into consideration. In addition, when considering DOACs, risk of bleeding from gastrointestinal primary tumors or genitourinary sites (e.g., nephrostomy tubes) should be taken into consideration as well. VKAs should be avoided in cases of intracranial malignancy and active chemotherapy as well as low platelet count due to difficulty in maintenance of INR.

- Consider preference for LMWH in acute cancer-associated VTE with high risk of bleeding when cancer site is either luminal GI tract, GU tract, or urinary bladder or has nephrostomy tubes in place. LMWH is also preferred over DOAC when a drug-drug interaction is possible with systemic therapies or when active GI mucosal ulcerative lesions are present [15•]. LMWH dose can be tapered in cases of renal insufficiency or recent bleeding. Anticoagulation with LMWH can be continued for platelet count < 50× 10^9/L but only with platelet transfusion [26].
- In patients with absolute contraindication to anticoagulation, IVC filter should be inserted for acute (< 1 month from index VTE) or subacute CAT (1–3 months) but not for chronic CAT (> 3 months) [27]. Follow up imaging [28] for thrombus progression is

advised with removal of the filter as well as resumption of anticoagulation after risk of bleeding is resolved [27].

Recurrent VTE

Another important pitfall to consider while anticoagulating cancer patients is recurrence of VTE. For a physician, balancing prevention of VTE recurrence against risk of bleeding is a challenging scenario especially in active cancer patients.

LMWHs vs VKAs Consistent with the results from the CLOT trial that showed a recurrence risk of 9% with LMWH vs 17% with VKA [29], the CATCH study reported a cumulative recurrence risk of 7.2% in LMWH vs 10.5% in VKA arm (hazard ratio [HR], 0.65 [95% CI, 0.41–1.03]; $P = 0.07$). The results are also similar to results from other recent trials which showed greater efficacy of LMWH compared with VKA therapy [30, 31]. A recently published 2018 Cochrane meta-analysis of five studies for VTE recurrence in CAT showed a significant reduction in recurrence rates with LMWH compared to VKA (RR 0.58, 95% CI 0.43 to 0.77; RD 53 fewer per 1000, 95% CI 72 fewer to 29 fewer; moderate certainty).

LMWHs vs DOACs As discussed earlier, two recent randomized trials have evaluated the efficacy of DOACs versus LMWHs. The HOKUSAI Cancer VTE trial concluded that edoxaban was non-inferior to LMWH in a composite outcome of recurrence and major bleeding; in particular, recurrence was lower with edoxaban versus dalteparin with rates of 7.9% and 11.3%, respectively (HR 0.71; 95% CI 0.48 to 1.06; $P = 0.09$) [24•]. The SELECT-D trial reported an even more significant absolute difference between rivaroxaban and dalteparin for recurrent VTE—4% (95% CI, 2 to 9%) vs 11% (95% CI, 7 to 16%), respectively [23]. Observational data from a claims database also suggests a significantly lower risk of recurrence and a similar risk of bleeding with rivaroxaban when compared to LMWH or warfarin [17].

Recommendation

Recent recommendations by Schulman et al. [32] for managing recurrent VTE in cancer patients focus on three phases namely acute, intermediate, and long-term phase.

(a) Acute phase (< 3 months)

- A therapeutic dose of LMWH should be used in patients who present with recurrence while on VKA, DOAC, or subtherapeutic dose of LMWH.
- The same therapeutic dose of LMWH can be continued, or it can be increased by 20–25% when patients present with recurrence while on therapeutic dose of LMWH.
- Thrombolysis or pharmacomechanic clot removal should be performed when recurrence causes massive VTE.

(b) Intermediate phase (3–6 months). All patients should be treated with same LMWH dose as in acute phase for the fourth month. After that, dose could be reduced by 25%.

(c) Long-term phase (> 6 months). LMWH (at the same dose as the intermediate phase) or DOAC or VKA should be used as long as cancer is active.

Thrombocytopenia and Anticoagulation

Thrombocytopenia (platelet count $< 100 \times 10^9$/L) is common in cancer patients particularly in those with hematologic malignancies and in patients receiving chemotherapy. Both thrombocytopenia and major as well as CRNM bleeding are related to an extent, but the risk of recurrent VTE does not resolve in thrombocytopenic patients [33, 34]. One retrospective cohort study by Kopolovic et al. documented that, in a 3-month follow-up period of 74 thrombocytopenic patients with the index VTE, 23 (31.1%) reported a recurrence or progression and 7 (9.5%) experienced both recurrence and bleeding events during this period. Fourteen of 23 (61%) were not on any anticoagulation, 6/23 (26%) had a reduced or prophylactic dose, and 3/23 (13%) were anticoagulated with a full therapeutic dose at the time of VTE recurrence [33]. A systematic review by Samuelson et al. showed a combined recurrence rate of VTE of 27% and major bleeding in 13%, irrespective of the treatment method used although the evidence base for this review was scarce [35].

Recommendation

Clinical recommendations for this issue rely best on the 2018 guidance statement from ISTH [36•].

(a) For patients with a platelet count $\geq 50 \times 10^9$/L and acute cancer-associated VTE (first 30 days after index event), LMWH should be used in its therapeutic dose for the first 30 days after the index event (when the recurrence risk is highest).

(b) For patients with a platelet count $< 50 \times 10^9$/L and acute cancer-associated VTE (first 30 days after index event) or subacute/chronic VTE (> 30 days since index event).

- LMWH should be used in its therapeutic dose with platelet transfusion in patients who have index event with high risk features for recurrence.
- LMWH should be used in a prophylactic or a 50% dose in patients having index event with low risk features and platelet count 25–50 × 10^9/L. If platelet counts drop below 25 × 10^9/L, it is advised to hold anticoagulation and start full-dose anticoagulation again when platelet count rises in the absence of another contraindication. IVC filter insertion should be inserted in patients with absolute contraindication to anticoagulation.

Renal Insufficiency

Renal insufficiency (RI) in cancer patients is frequent, and it is a common practice to alter anticancer treatment doses and medications due to RI. A creatinine clearance (CrCl) < 60 mL/min was present in 16.6%, 16.1%, and 15% patients in the Renal Insufficiency and Anticancer Medications (IRMA) ($n = 4684$) study [37], the Belgian Renal Insufficiency and Anticancer Medications (BIRMA) ($n = 1218$) study [38], and the CATCH study [39•], respectively. According to the IRMA study, almost 80% patients with RI were on at least one medication that needed dose adjustment due to RI [37]. Furthermore, certain nephrotoxic antineoplastic medications can worsen baseline RI [40]. RI can lead to clinically relevant abnormalities in hemostasis which can increase the risk of both bleeding and thrombosis in patients [41]. Bioaccumulation of anticoagulants can occur as a result of decreased renal clearance. This is especially true for renally cleared agents in the LMWH and VKA groups and thus increases the risk of bleeding [42].

LMWHs vs VKAs A posthoc subgroup analysis of the CLOT trial by Woodruff et al. reported that dalteparin and warfarin were comparable in terms of safety, i.e., the risk of bleeding in renally impaired cancer patients on anticoagulation, but dalteparin was more effective in preventing recurrent VTE [43]. The CATCH study subgroup analysis in patients with RI also reported comparable outcomes for both safety and efficacy of tinzaparin vs warfarin but showed almost twofold higher risk of recurrence and bleeding overall in patients with RI compared to the full CATCH study population [39•].

Recommendation

Current guidelines recommend using LMWH for CAT in patients with RI but with caution given the known increase in risk of bleeding as well as increased recurrence. There is a need to assess baseline renal function at the initiation of anticoagulation. Data regarding safety and efficacy of DOACs in this population are awaited.

LMWH is superior to VKA in these patients [39•, 44, 45].

Nausea and Vomiting

Nausea and vomiting are common in cancer patients and can impact the effect of orally administered anticoagulants. At a time when DOACs are being studied as reliable alternatives to LMWH, it is important to consider the effect of ongoing nausea and vomiting on efficacy of this class of agents. A recent expert consensus statement by Riess et al. provided the following recommendations for patients on anticoagulation with DOACs and acute or prolonged nausea/vomiting [46••].

- Patients on anticoagulation with DOAC who present with acute (< 24 h) nausea/vomiting
  - (a) Causes of nausea/vomiting and risk of recurrence of nausea/vomiting and thromboembolism should be assessed; if at high risk for either, LMWH should be used and DOAC should be resumed only after it resolves.
  - (b) If nausea/vomiting recurs 2 h after the use of DOAC, one dose equivalent of parenteral LMWH should be added, but no change is required if it recurs > 2 h after the intake of a DOAC.
- Patients on DOAC presenting with prolonged (< 24 h) nausea/vomiting
  - (a) The causes of nausea/vomiting and the risk of thromboembolism recurrence should be assessed
  - (b) In presence of risk for recurrent VTE, DOAC should be stopped until nausea/vomiting resolves and a parenteral LMWH should be administered.
  - (c) Antiemetics should be ordered for all patients, consistent with international guidelines.

Patient Adherence to Anticoagulation

There are concerns about patient compliance with parenteral agents. From data collected between 2009 and 2014, we reported that of 52,911 patients on anticoagulation, warfarin was prescribed in 50%, LMWH in 40%, and other anticoagulants in 10% patients. During the first 6 months after VTE, 44% patients who began LMWH shifted to warfarin or others and 28% who began warfarin shifted to LMWH or others. Thus, more patients persist with oral anticoagulants than injectables possibly due to concerns of cost and self-injection [47]. In

another similar dataset, we found that only 25% of cancer patients were treated with LMWH monotherapy despite guideline recommendations [48•]. Patient persistence with anticoagulation was reported as 37% with LMWH and 61% with oral agents. Results from a recent cohort study showed that 51% patients discontinued LMWH therapy within 180 days on initiation and 21% said it was due to side effects [20].

In addition to patient adherence issues, it should be noted that physician compliance with guidelines for treatment of cancer-associated VTE is suboptimal, although this may partly be related to patient preference and cost issues. The TROPIQUE study showed that though 98% patients received prescriptions for more than 3 months, only 55.3% patients were prescribed LMWH according to guidelines [49]. Recent results show a compliance of 66.4% (RIETE registry till 2013) [50], 59% (CARMEN study) [51], and 67.1% (prospective study by Matzdorff et al.) [52] which is an improvement from prior studies—40% (Kaatz et al.) [53], 43.2% (Rahme et al.) [54], 25% (Delate et al.) [55], and 34% (Spirk et al.) [56]. A French cohort study divided the treatment duration in three stages T1 (≤ 10 days), T2 (10 days–3 months), and T3 (3–6 months) and showed guideline adherence of 55%, 31%, and 34%, respectively, during each stage with an overall adherence of 52.8% [57]. This study also showed that the presence of pulmonary embolism or metastatic malignancy was associated with more compliance. Noble et al. who reported on patient preference showed factors in order of decreasing significance included interference with cancer treatment, efficacy, risk of major bleeding, administration form, blood monitoring, risk of minor bleeding, and frequency of administration [52].

Drug-Drug Interactions with Anticancer Drugs

Drug-drug interactions (DDI) are an area of major concern in cancer patients on non-surgical anticancer therapy. One such major interaction can be with anticoagulants since the spectrum of chemotherapy, antiangiogenic agents, adjuvant chemotherapy, and hormonal therapy all can have a prothrombotic effect in cancer patients. Anticancer drugs often have a very narrow therapeutic index, and it makes the management even difficult.

LMWH is compatible with most anticancer drugs, but warfarin and DOACs have significant DDI with anticancer drugs. A pilot study involving a total of 64 patient reported that 33% of DDI in cancer patients receiving anticancer drugs is due to warfarin [58]. A multitude of chemotherapeutic agents can cause drug-drug interaction with warfarin which has been mostly reported in the form of case reports and does not provide conclusive clinical evidence of adverse events with specific anticancer agent in this population. Capecitabine [59–61] and cisplatin [62] are the drugs which have been reported most frequently for a DDI with warfarin. The emerging concern is the use of DOAC in patients receiving chemotherapy. Every DOAC is a substrate of P-glycoprotein, but not all DOACs are a substrate of CYP3A4 metabolism. Edoxaban is less significantly metabolized by CYP3A4 pathway, and dabigatran is not a substrate of the same. They are the ones that are excreted renally more than hepatically [63]. Table 1 illustrates the pharmacokinetic interactions between DOACs and anticancer drugs [64]. There are also notable DDI between DOAC and commonly prescribed non-chemotherapeutic agents in cancer patients depending upon the P-glycoprotein and/or CYP3A4-induced metabolism. The common examples include ketoconazole, verapamil, cyclosporine, clarithromycin, dronedarone, rifampin, ritonavir, and amiodarone [63]. Thus, P-glycoprotein and/or CYP3A4 inducers may increase the risk for recurrence of VTE by decreasing the DOAC concentration, whereas the inhibitors may increase DOAC concentrations and thereby increase the risk of bleeding. However, most of the studies report pharmacokinetic interactions that were performed on healthy volunteers. There have been very few studies that have drawn data for clinically relevant DDI of anticancer medications with anticoagulants and their pharmacodynamic effects in cancer patients.

Table 1 Pharmacokinetic interactions of direct oral anticoagulants with anticancer agents

	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Anticancer treatment that may increase plasma levels of the anticoagulant				
Lapatinib	AB	AB	(A)B	B
Tamoxifen	AB	AB	(A)B	B
Imatinib	A	A	(A)	
Nilotinib	A	A	(A)	
Dasatinib	A	A	(A)	
Erlotinib	A	A	(A)	
Sunitinib	A	A	(A)	
Sorafenib	AB	AB	(A)B	B
Bicalutamide	A	A	(A)	
Anticancer treatment that may decrease plasma levels of the anticoagulant				
Doxorubicin	D	D	D	D
Vinblastine	D	D	D	D
Enzalutamide	C	C	C	
Dexamethasone	CD	CD	(C)D	D

From Voigtlaender M, Langer F. Management of cancer-associated venous thromboembolism—a case-based practical approach. *Vasa*. 2018;47 (2):77–89. https://doi.org/10.1024/0301-1526/a000684, with permission from Hogrefe AG

A CYP3A4 inhibitor, *B* P-glycoprotein inhibitor, *C* CYP3A4 inducer, *D* P-glycoprotein inducer

Conclusions

Management of venous thromboembolism in cancer patients requires an individualized approach and anticipation of potential pitfalls. These include bleeding and concern for recurrence of VTE and can further be complicated by thrombocytopenia, renal insufficiency, patient and physician adherence, nausea-vomiting, and drug-drug interactions. Emerging data regarding DOACs has changed paradigms for treatment, with an emphasis on understanding bleeding risk in patients. Ongoing studies are evaluating identification of biomarkers for better prediction of cancer-associated thrombosis and the role of anticoagulation in primary prevention.

Compliance with Ethical Standards

Conflict of Interest Harsh K. Patel declares that he has no conflict of interest.

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Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines)

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- • Of importance
- •• Of major importance

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