

Venous thromboembolism and palliative care

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ABSTRACT

The management of cancer-associated thrombosis (CAT) is largely informed by data from adequately powered randomised control trials. However, their exclusion criteria have invariably rendered the study populations unrepresentative of those seen day-to-day by palliative care practitioners.

Recent observational data has given insights into the unique challenges of CAT management within the palliative care setting including the natural history of thrombosis in advanced cancer and end-of-life decision making around anticoagulation

Despite developments and some on-going uncertainties, one constant remains; the patient and their experiences. We should, wherever possible, involve them in the decision-making process particularly where the evidence is lacking. By appreciating the values and concerns of our patients, we shall be able to plan care that most meets their needs.

Introduction

Venous thromboembolism (VTE) comprising of deep vein thrombosis (DVT) and pulmonary embolus (PE) occurs in one in 1,000 adults, but will increase with age, reduced mobility and concurrent chronic illness including cancer. The management of VTE in patients with advanced metastatic cancer and life limiting non-malignant illness has changed considerably, over the past 15 years, from a nihilistic philosophy that a sudden fatal PE should be welcomed, to a more individualised and tailored approach to thrombus prevention and treatment. Challenges of managing VTE in palliative care include; defining the palliative population, recognition of VTE, diagnosis of VTE, treatment of VTE and length of treatment.¹ This paper shall primarily focus on the current evidence for managing cancer-associated thrombosis (CAT) with particular emphasis on patients with advanced or metastatic disease. It will consider challenges facing clinicians working in palliative care and hospice teams but will also offer guidance to teams involved in supportive care of patients with metastatic disease.

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Presentation and diagnosis

Despite a high prevalence of VTE in advanced cancer, CAT is notoriously under reported in hospices and specialist palliative care units (SPCU). In part, this reflects the myriad of pathologies seen in advanced disease, which have presenting symptoms similar to those of VTE.² Dyspnoea is a common symptom and conditions such as anaemia, pulmonary oedema, infection and pleural effusion may be considered before pursuing a diagnosis of PE. Similarly, swollen legs may be attributed to hypoalbuminaemia, left ventricular failure or pelvic lymphadenopathy before considering DVT. Within stand-alone SPCUs/hospices, where access to definitive radiology support requires patient transfer, clinicians may be less likely to pursue and diagnosis of VTE if other pathologies are possible.

While D-dimers are routinely used in the diagnostic work up for VTE, they have little utility in the cancer setting. D-dimers are specific cross-linked fibrin derivatives produced when fibrin is degraded by plasmin.³ Concentrations are therefore raised by thrombolysis, making them a highly sensitive indicator for VTE. They

Key points

The current data supports low molecular weight heparin as the first line management of cancer associated venous thromboembolism.

New data shows that direct-acting oral anticoagulants (DOACs) have a lower rate of venous thromboembolism recurrence but this comes at an expense of major bleeding.

Major bleeding on DOACs is most marked in gastrointestinal and urothelial tumours.

Patients with poor performance status and short prognosis are unlikely to benefit from thromboprophylaxis.

Consider stopping anticoagulation in patients with advanced cancer as death approaches.

KEYWORDS: Cancer associated thrombosis, venous thromboembolism, palliative, hospice, low molecular weight heparin, DOACs ■

have a high sensitivity for VTE but low specificity since levels may be raised in the presence of recent surgery, liver disease, cancer, pregnancy and infection. Although D-dimer values are an important exclusory test for the diagnosis of VTE, with a negative predictive value of close to 100%, they have no role in the palliative care setting.

The definitive confirmatory investigation for DVT and PE is compression ultrasonography and computed tomography pulmonary angiography, respectively.^{4,5} Both investigations are relatively easy to access and well tolerated by patients. However, for stand alone hospice and SPCU inpatients, the logistics of organising the tests, which may be undertaken at another institution, may be too difficult for some patients. This has been known to impact on clinicians' threshold for investigating for VTE especially if other causes can be attributed.⁶

Treatment

While palliative care does not aim to prolong life, it does not aim to shorten it either. There are those of the opinion that 'A large PE may be a nice way to go' implying that a sudden asymptomatic death due to PE is arguably less distressing or burdensome than a prolonged decline due to progressive cancer. However, the concept of fatal PEs being asymptomatic is an erroneous one. A post-mortem study of patients in whom pulmonary embolus was confirmed as the cause of death suggested that a sudden asymptomatic death occurred in only 10% of patients. The majority have prolonged symptomatic deaths lasting an average of 2 hours, dominated by dyspnoea, tachycardia and distress.⁷

Current clinical guidelines recommend weight adjusted low molecular weight heparin (LMWH) as the first line treatment of CAT, since it has demonstrated superiority over warfarin with respect to preventing recurrent VTE, without an increase in bleeding complications.⁸ In addition, the use of warfarin is particularly challenging in many patients receiving chemotherapy due to drug–drug interactions rendering the international normalised ratio unstable. Conversely, LMWH has fewer drug–drug interactions and rarely requires monitoring.

It is important to note that the trials evaluating warfarin versus LMWH in CAT excluded patients with a life expectancy of less than 3 months, poor performance status, increased bleeding risk, renal impairment, weight <40 kg, thrombocytopenia and other comorbidities common in palliative patients. Within these randomised trials, the prevalence of metastatic disease, a possible palliative indicator, ranged from approximately 40 to 70%.⁹ However, several case series of patients under palliative care teams have supported its use in patients with poorer performance status or prognosis.

Since LMWH is administered as a daily subcutaneous injection, there are concerns that this form of administration may have a negative impact on patients' quality of life and be a less acceptable intervention than oral alternatives. Qualitative studies suggest that patients find LMWH acceptable within the context of their cancer journey and quickly adapt to the daily routine of self-injection.^{10,11}

Direct-acting oral anticoagulants and cancer

Two randomised controlled trials have compared a direct-acting oral anticoagulant (DOAC) with LMWH in the treatment of CAT. The Hokusai VTE-cancer study compared 5 days of LMWH

followed by edoxaban 60 mg once daily with dalteparin at a dose of 200 IU/kg for 1 month followed by dalteparin 150 IU/kg in cancer patients with VTE.¹² The primary outcome was a composite of recurrent VTE and major bleeding. One-thousand and forty-six patients were recruited. Edoxaban demonstrated non-inferiority with dalteparin with a primary-outcome event in 67 of the 522 patients (12.8%) in the edoxaban group with 71 of the 524 patients (13.5%) in the dalteparin group (hazard ratio (HR) = 0.97; 95% confidence interval (CI) = 0.70–1.36; $p=0.006$ for non-inferiority; $p=0.87$ for superiority). It appears that edoxaban results in fewer recurrent VTE events, at the expense of more major bleeding episodes. Recurrent VTE occurred in 41 patients (7.9%) in the edoxaban group and in 59 patients (11.3%). Major bleeding occurred in 36 patients (6.9%) in the edoxaban group and in 21 patients (4.0%). Major bleeding was higher in gastrointestinal (13.1%) and urothelial (7.9%) cancers and it would seem reasonable to avoid DOACs in such cancers.

The SELECT-D study, compared rivaroxaban with dalteparin for the treatment of CAT.¹³ While underpowered, its results were similar to edoxaban. The VTE recurrence rate at 6 months was 11% (95% CI = 7–17%) for patients on dalteparin and 4% (95% CI = 2–9%) for patients on rivaroxaban. Major bleeds were similar across trial arms but there were more clinically relevant non-major bleeds (CRNMBs) on the rivaroxaban arm; five bleeds (2%; 95% CI = 1–6%) on dalteparin compared with 28 bleeds (13%; 95% CI = 9–19%) on rivaroxaban.

When considering DOACs in the palliative care setting, caution has been advised in the frail and elderly, with underlying hepatic dysfunction, and with impaired renal function (with avoidance of DOACs altogether in those with a creatinine clearance less than 30 mL/min). Another important consideration is the multiple drug–drug interactions that exist with these agents, leading to increased or reduced DOAC plasma levels. While subject to fewer interactions than warfarin, DOACs are particularly sensitive to medicines, which inhibit P-glycoprotein or cytochrome P450 3A4 (CYP3A4).¹⁴ These include chemotherapies and supportive care medicines commonly used in oncology, which include chemotherapeutic and immunosuppressive agents, hormonal therapies, tyrosine kinase inhibitors and dexamethasone (Table 1).

Challenging scenarios

Up to 21% of CAT patients are managed outside of the standard treatment of weight adjusted LMWH.¹⁵ These include patients with recurrent VTE despite anticoagulation, patient with thrombocytopenia, and those with bleeding complications. The management of such cases is covered in a guidance document recently published by the International Society for Thrombosis and Haemostasis Scientific Sub-Committee for malignancy and haemostasis, which is summarised in Table 2.¹⁶

Anticoagulation in the last days of life

CAT guidelines recommend indefinite anticoagulation for patients with ongoing active cancer but none of them address management of anticoagulation as death approaches. Cancer patients are highly thrombotic at the end of life, most probably due to a combination of disease progression, immobility, dehydration and infection. In a recent case series of 214 patients with CAT who died over a 2-year period, 50% continued LMWH until death and 11% up to 7 days prior to

Table 1. Common drug–drug interactions with direct-acting oral anticoagulants.¹⁴

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Interaction effect	P-glycoprotein	P-glycoprotein CYP3A4	P-glycoprotein CYP3A4	P-glycoprotein
Increases DOAC plasma levels^a		Dasatinib Imatinib	Dasatinib Imatinib	
	Lapatinib Nilotinib Sunitinib Tamoxifen	Lapatinib Nilotinib Sunitinib Tamoxifen	Lapatinib Nilotinib Sunitinib Tamoxifen	Lapatinib Nilotinib Sunitinib Tamoxifen
Reduces DOAC plasma levels^b	Dexamethasone Doxorubicin Enzalutamide Vinblastine	Dexamethasone Doxorubicin Enzalutamide Vinblastine	Dexamethasone Doxorubicin Enzalutamide Vinblastine	Dexamethasone Doxorubicin Enzalutamide Vinblastine

DOAC = direct-acting oral anticoagulants.

a = Drugs that inhibit P-glycoprotein or CYP3A4 can increase DOAC levels

b = Drugs that induce P-glycoprotein or CYP3A4 can lower DOAC levels.

death.¹⁷ In those who discontinued anticoagulation earlier, there were no reported symptoms attributable to recurrent VTE. Major and CRNMB were experienced by 7% of those who continued LMWH, to or within 7 days of death. Typically, symptomatic DVT and PE manifest themselves approximately 7 and 21 days, respectively, after the initial pro-thrombotic

insult.¹⁸ If this holds true for patients with advanced cancer, one could stop anticoagulation for patients in whom prognosis is limited to days, thereby minimising bleeding without a recurrence of thrombotic symptoms. If patients develop VTE in the agonal phase, end of life medicines could be used to manage symptoms without risking haemorrhage.

Table 2. Management of challenging cases of cancer-associated thrombosis¹⁶**Recurrent VTE despite anticoagulation**

- > If on warfarin, switch to therapeutic LMWH.
- > If already on LMWH, increase dose by 25 % or increase back up to therapeutic weight adjusted dose if they are receiving non-therapeutic dosing.
- > If no symptomatic improvement use peak anti-Xa level to estimate next dose escalation.

Management of CAT in thrombocytopenia

- > For platelet count $>50 \times 10^9 \text{ L}^{-1}$ give full therapeutic dose LMWH.
- > For acute CAT and platelet count $<50 \times 10^9 \text{ L}^{-1}$:
 1. full anticoagulation with platelet transfusion to maintain platelet count $>50 \times 10^9 \text{ L}^{-1}$
 2. if platelet transfusion is not possible consider retrievable IVC filter.
- > For subacute or chronic CAT and thrombocytopaenia (platelet count $<50 \times 10^9 \text{ L}^{-1}$):
 1. reduce therapeutic dose by 50 % or use prophylactic dose for platelet count $25\text{--}50 \times 10^9 \text{ L}^{-1}$
 2. omit LMWH if platelet count $<25 \times 10^9 \text{ L}^{-1}$.

Bleeding while anticoagulated

- > Assess each bleeding episode to identify bleeding source, severity, impact and reversibility.
- > Provide supportive measures to stop bleeding, including transfusion where indicated.
- > For a major or life-threatening bleeding episode, withhold anticoagulation:
 1. consider IVC filter insertion in patients with acute or subacute CAT with a major or life-threatening bleeding episode
 2. do not consider IVC filter insertion in patients with chronic CAT
 3. once bleeding resolves, remove retrievable filter (if inserted) and resume/initiate anticoagulation.

CAT = cancer-associated thrombosis; IVC = inferior vena cava; LMWH = low molecular weight heparin; VTE = venous thromboembolism.

Primary thromboprophylaxis

The prevention of 'hospital acquired thrombosis' is a healthcare priority in many countries, yet remains unclear in SPCUs and hospices. Clinical guidelines suggest that in the absence of contraindications, primary thromboprophylaxis is recommended for acutely ill hospitalised medical patients, including those with underlying cancer. Few SPCUs follow thromboprophylaxis policies and prophylactic LMWH is rarely initiated or continued on admission. Reasons for not following guidelines, include a view that VTE is not a particular problem and that the studies which inform prophylaxis were conducted in an unrepresentative population using outcome measures of limited utility in the hospice or SPCU.¹⁹

A recent multicentre observational study of 1,199 patients (90% of whom had a cancer diagnosis) admitted to 22 hospices/SPCUs demonstrated a low incidence of VTE but a high incidence of clinically relevant bleeding (9.8%). Multivariate analysis identified that bleeding was associated with thromboprophylaxis ($p=0.04$, HR = 1.48 (1.02–2.15)), suggesting that the bleeding risks of VTE prophylaxis might outweigh the benefits in this population.²⁰

The Hospice Inpatient Deep Vein Thrombosis Detection study has recently been published and further challenges the perceived benefit of pharmacological thromboprophylaxis.²¹ In this prospective longitudinal observational study, 343 cancer patients underwent bilateral femoral vein ultrasonography on admission and weekly until death or discharge. Patients were excluded if admitted for terminal care (estimated prognosis <5 days). Patients had a mean Australian-modified Karnofsky Performance Score of 49 and survival of 44 days, indicating a highly dependent and poor prognosis cohort. Femoral DVT was observed in 28% of participants with minimal symptoms and there was no difference in survival in those with or without DVT. These data challenge the utility of thromboprophylaxis in patients of poor performance status and prognosis although its role in selected patients of good performance status, with temporary elevations of thrombotic risk factors remains to be clarified.

Conclusion

As people live longer with metastatic disease and receive palliative chemotherapies into older age, there has been a blurring around the margins of what constitutes palliative, supportive and end of life care when managing venous thromboembolism. Cancer associated thrombosis will continue to be challenge for any team looking after patients with advanced metastatic cancer and life limiting non-malignant illness. With the increasing heterogeneity of malignant disease, breadth of anticancer treatments and available anticoagulants it is highly unlikely that a one size fits all approach to CAT management will exist in the future. Just as anticancer treatments have become so individualised that their indications may be based upon molecular biomarkers, it is reasonable to expect other aspects of cancer management to be individualised, particularly when considering advanced disease where quality of life takes primacy over longevity. ■

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