Research Review™
EDUCATIONAL SERIES

Prevention and management of cancer-associated thrombosis

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Abbreviations used in this issue

CT = computed tomography
DOAC = direct oral anticoagulant
DVT = deep vein thrombosis
HIT = heparin-induced thrombocytopenia
INR = international normalised ratio
IVC = inferior vena cava
LMWH = low molecular weight heparin
PE = pulmonary embolism
RCT = randomised controlled trial
SC = subcutaneous
UFH = unfractionated heparin
VKA = vitamin K antagonist
VTE = venous thromboembolism

This review is intended as an educational resource for health professionals. It covers the recommendations for the prevention and management of VTE, specifically in patients with cancer, with a focus on how LMWHs compare with other anticoagulants (e.g. VKAs) including the newer oral anticoagulants. Summaries of reviews supporting the recommendations are included, along with commentary from local experts. We hope you find this Educational Series an enlightening and stimulating read, and we would enjoy hearing your thoughts and ideas. This review is sponsored by an educational grant from Sanofi.

Introduction

VTE, which includes DVT and PE, is a potentially life-threatening condition with significant associated morbidity and mortality.[1,2] Among Western populations, VTE is the third most common circulatory disorder. Virchow's triad (figure 1) describes the basic pathology of thrombosis: venous stasis, endothelial damage and hypercoagulability.[3] Of these, the latter (or the intrinsic hypercoagulable state) is the greatest contributor to the increased VTE risk seen in patients with cancer, with tumour cells possessing a number of prothrombotic properties, including procoagulant mechanisms, fibrinolytic mechanisms, cytokine release and tumour cell to host cell interactions.

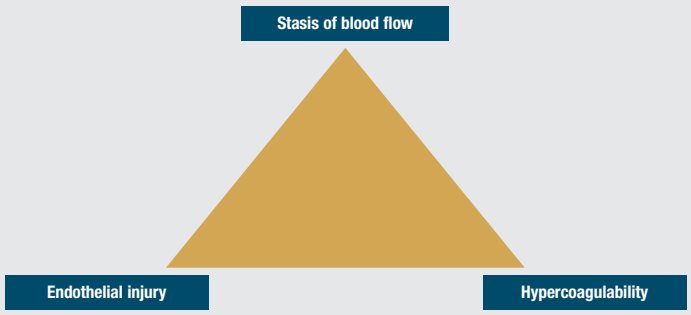

Figure 1. Virchow's triad of thrombosis

VTE risk increased in cancer patients

Thrombosis is a long- and well-established complication for patients with cancer, and incidence of VTE in patients with cancer has increased over recent decades.[3] This increased incidence may reflect the use of newer anticancer agents with prothrombotic properties, better disease detection with more sensitive imaging techniques or increased detection of incidental VTE during planned staging CT scans.[4] While it is generally reported that >1% of patients with cancer experience VTE, it has recently been reported that ~3% of patients with cancer have incidental PE.[5] The risk of VTE is >3-fold greater compared with the general population, and around 20–30% of first VTEs occur in patients with cancer.[1,2,6] However, VTE is likely to be triggered by multiple pathways among patients with different cancers, and annual incidences have been shown to vary widely (0.5–20%) depending on cancer type. For example, some cancers are associated with increased platelet and leucocyte numbers, which increase VTE risk. Disease stage and treatment modality also impact on VTE risk (figure 2). As cancer treatments improve, so do the numbers of cancer survivors and consequently numbers of individuals at risk of VTE.

In general, the VTE risk is greatest during the first few months after a cancer diagnosis.[7] This may be confounded by the fact that imaging may be more intensively performed during the early stages of the disease process, and VTE will therefore be more likely to be found compared with later in the disease process where imaging is less frequent. Moreover, cancer surgeries and some pharmacotherapeutic agents are themselves risk factors for VTE – surgery doubles the VTE risk. As such, careful targeting of VTE prophylaxis to the highest risk patients and also at the most appropriate times within their disease course could therefore help improve cancer survival. As the risk of VTE is

increased in patients with cancer, patients presenting with unprovoked VTE may have undiagnosed cancer. As the overall prevalence of this is low and routine screening, in particular imaging, is not warranted, further investigations to identify cancer should be considered if there is suspicion of cancer, e.g. bilateral DVT, high D-dimer level (especially for thrombotic load), early VTE recurrence and clinical factors.[3,8]

Other factors contribute to the risk of VTE in patients with cancer (figure 2). Thrombophilias, such as factor V Leiden and prothrombin G20210 mutations, or the rarer deficiencies in antithrombin, protein C or protein S, influence a patient's predisposition to VTE to varying degrees.[1] It is also well-known that immobilisation among hospitalised patients increases VTE risk, and this is an additional consideration for cancer patients who require surgery and those in whom their cancer type/stage has reduced their mobility.

Among biomarkers of a hypercoagulable state that may indicate if a patient is at increased risk of VTE, D-dimer is usually considered the most robust, although its specificity is decreased in older patients.[1] Other potential biomarkers include TATc (studied in abdominal cancer), prothrombin fragments 1+2 (possibly in combination with D-dimer, although not yet validated in clinical studies), factor VIII, soluble P-selectin, haemoglobin level/erythropoiesis-stimulating agents and leucocyte and platelet counts.[1,9,10] Tumour genetic profiles are a recently identified potentially important risk factor for thrombosis in patients with cancer, and testing for mutations could therefore become useful in risk assessment in the future; e.g. *KRAS* mutations have been shown to be associated with an increased risk of VTE in patients with metastatic colorectal cancer.[11]

VTE burden in cancer patients

VTE is the most common cause of death in patients with cancer after cancer-related surgery.[3] The 1-year survival rate among patients with cancer who experience a VTE is ~12%, and median overall survival is 3.5–13 months versus 4–25 months for cancer patients without VTE – the ranges of these values are explained mainly by cancer site.[4] VTE recurrence and VTE-related bleeding event rates are also higher among patients with cancer than those without cancer.

VTE in patients with cancer is also associated with increased hospital length of stay, reduced quality of life and interruptions/delays in anticancer treatments.[1,4,12] In addition, the average total adjusted cost in the US of managing a patient with lung cancer who had VTE has been reported as ~40% greater than for a lung cancer patient without VTE, due mainly to hospitalisation costs of initial and recurrent VTE events – this is consistent with other data, albeit limited, reporting a sizeable financial burden of VTE in patients with cancer.

Together, the available information highlights the importance of adopting evidence-based protocols for preventing and managing VTE in patients with cancer, with the aims of reducing the clinical and economic burdens on patients, healthcare systems and society.

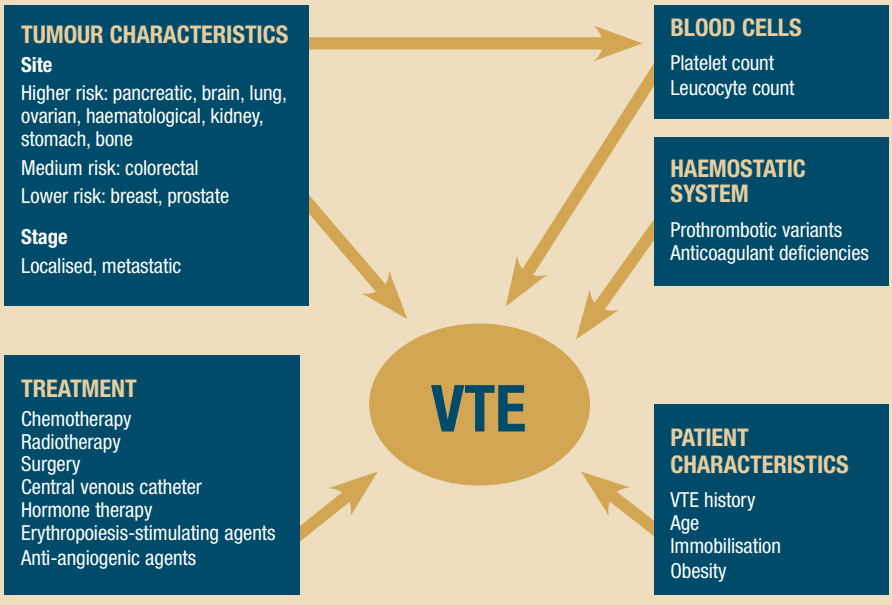

Figure 2. Risk factors for thrombosis in patients with cancer[1,2]

Managing VTE in cancer patients

Preventing VTEs (including recurrence) and managing VTEs when they occur are both important aspects of managing patients with cancer. As there are risks associated with anticoagulants, it is important to identify patients at highest risk of VTE before administering such agents as a preventive strategy. If a patient with cancer experiences VTE, it is important that appropriate treatment is administered to treat the thrombus and restore haemostasis. A VTE event is also an important predictor of recurrent VTE, and appropriate prophylaxis is also required after an initial event. There is historical evidence that patients with cancer may be twice as likely to bleed during anticoagulant therapy and have three times the risk of VTE recurrence compared with patients without cancer.[13] There are a number of anticoagulants available for preventing and treating VTE.

Low-molecular weight heparins (LMWHs)

LMWHs are derived from UFH by depolymerisation and have gradually replaced UFH for most indications due to less variable pharmacological properties that are associated with UFH's highly variable anticoagulant response.

Enoxaparin sodium (Clexane® and Clexane Forte®) is a well-established funded LMWH in NZ with high anti-Xa activity (~100 IU/mg) and low anti-IIa or antithrombin activity (~28 IU/mg).[14] It is completely absorbed after SC injection, with maximum plasma anti-Xa activity occurring in 3–5 hours. Dosage reductions are needed in severe renal impairment (without anti-XA activity monitoring), and close monitoring is recommended for milder renal impairment. No dose adjustment is needed for elderly patients with normal renal function when used for VTE indications.

Dalteparin sodium (Fragmin®), a Special Authority funded LMWH, accelerates the neutralisation rate of activated coagulation factors, mainly Xa, but also XIIa and kallikrein by antithrombin.[15] Dalteparin is 90% absorbed after SC injection and has a half-life of 3–4 hours. In severe renal impairment, monitoring of anti-XA levels (target 0.5–15 IU/mL) is recommended to determine the optimal dose. Dose reductions are also needed in a patient who has cancer, acute symptomatic VTE and chemotherapy-induced thrombocytopenia (platelet count 50–100 × 10^9/L) until the platelet count has recovered. Caution is recommended during dalteparin use in elderly patients, especially those aged >80 years due to their increased risk of bleeding.

Tinzaparin, an alternative LMWH available in NZ, is not on the Pharmac schedule.[16]

Fondaparinux is an inhibitor of factor Xa activity that is chemically related to LMWHs. It undergoes rapid, complete absorption following SC administration and has a half-life of 17–21 hours.[17] It is mostly excreted unchanged in the urine. It is contraindicated in severe renal impairment and needs to be used with caution in patients with renal impairment of lesser severity. It is not routinely used in NZ for patients with VTE.

Vitamin K antagonists (VKAs)

Warfarin is an anticoagulant that acts by inhibiting vitamin K-dependent coagulation factor synthesis, leading to sequential dose-dependent depression of factors VII, IX, X and II activities.[18] Warfarin is almost completely absorbed after oral administration and its half-life is 2.5 days, with the peak anticoagulant effect potentially delayed by 72–96 hours. It is metabolised in the liver and excreted in the urine. Warfarin doses must be individualised according to one-stage prothrombin time, standardised as the INR. Warfarin is contraindicated in the first and third trimesters of pregnancy. The elderly may be more susceptible to the effects of warfarin, resulting in an increased risk of haemorrhage. Lower maintenance doses, weight for weight, than those usually recommended for adults may be required for elderly patients.[19]

Direct oral anticoagulants (DOACs)

The DOACs consist of the direct Xa inhibitors, rivaroxaban and apixaban, and the direct thrombin inhibitors, dabigatran and bivalirudin; only rivaroxaban and dabigatran are on the PHARMAC schedule – rivaroxaban only via special authority for prophylaxis after hip and knee joint replacement surgery.[16,20] DOACs appear attractive due to ease of administration, and there is recent RCT evidence raising the suggestion that apixaban may be useful for treating VTE in patients with cancer; however, this was a subgroup analysis with very small numbers.[21] There are also unaddressed issues regarding the use of DOACs in patients with cancer, including: i) small numbers of highly selected patients with cancer in the pivotal RCTs supporting their use; ii) use of warfarin or placebo as comparators rather than LMWHs in these RCTs; iii) unknown importance of interactions with anticancer agents; iv) bioavailability issues in patients with cancer who have gastrointestinal problems; and v) lack of reversibility agents.[22] More evidence from RCTs comparing them with LMWHs for VTE prevention and treatment in patients with cancer is needed. Note, DOACs are also often referred to as NOACs (nonvitamin K, new or novel oral anticoagulants, with the 'new' or 'novel' definitions becoming obsolete as time passes).

Mechanical prophylaxis

Graduated compression stockings and intermittent pneumatic compression devices have a well-established role in the prevention and management of VTE, particularly in orthopaedic surgery.[23] There are few data on their use in patients with cancer, but extrapolation of data from other stroke and surgical studies suggests that while insufficient on its own, mechanical thromboprophylaxis is likely to be a useful addition to pharmacoprophylaxis in patients with cancer and those with a significant risk of bleeding.

Guidelines for preventing and treating VTE in patients with cancer

There are a number of individual variables to consider when determining the best strategy for preventing or managing VTE in patients with cancer, meaning there is no one-size-fits-all approach. There are several guidelines available for the specific management of cancer-associated thrombosis, including guidelines from the Australia and New Zealand Working Party in the Prevention of Venous Thromboembolism published in 2012, and on most points, these guidelines are consistent with each other (see Tables 1a–c on pages 5–6).[23–33] The guidelines consistently favour LMWHs over VKAs and other anticoagulants for patients requiring VTE primary prophylaxis, treatment or secondary prophylaxis, with most suggesting UFH or fondaparinux as an alternative if LMWHs are not suitable. Some agents listed in international guidelines are not funded or available in NZ – only agents available in NZ are included in this publication.

Risk assessment

VTE risk assessments are now commonplace in NZ hospitals for surgical and some medical patients. All patients with active cancer should periodically undergo assessment for VTE risk.[31] There are a number of risk prediction models available. Tools like the Padua Prediction Score are designed for use in all hospital inpatients, with active cancer an important component in determining risk.[34] The extended 'Khorana score' is a VTE risk assessment model specifically for ambulatory patients with cancer.[35] It takes into account cancer site, erythropoiesis-stimulating agents, platelet count, leucocyte count and body mass index, and stratifies risk into low, medium and high. Another score specific for patients with cancer is the Ottawa score, which considers gender, VTE history and cancer type and stage.[1] ASCO recommends the Khorana score; however, only very few patients categorised as high risk by this tool experience a VTE, and as such it has not been widely adopted by oncologists, due mainly to lack of reliable, validated risk assessment models.

LMWHs first choice for primary prophylaxis…

Patients with cancer admitted to medical or surgical wards should receive pharmacological chemoprophylaxis, unless the benefits are outweighed by bleeding risk (see Table 1a).[23,24,26,29,31,33,36,37] Patients with cancer undergoing surgery should receive pharmacological thromboprophylaxis for 7–10 days, with extended prophylaxis with LMWH considered for high-risk patients and those undergoing abdominal or pelvic surgery.

All cancer outpatients should be risk assessed, although routinely such patients are not high risk and do not require thromboprophylaxis.[23,25,29,31,33,36] Patients with multiple myeloma should undergo risk assessment. Those at low risk could be offered low-dose aspirin. The high-risk group, including those on thalidomide or lenalidomide combination therapy, should be offered thromboprophylaxis with LMWH or warfarin. Of note, primary prophylaxis with LMWH in the outpatient setting is currently not funded in NZ. Other risk factors in myeloma include newly diagnosed disease status, immobility due to pain or recent surgery, indwelling venous catheters and plasmacytoma causing venous compression. Routine anticoagulant use in cancer is not recommended for: i) catheter-related thrombosis prophylaxis; ii) patients with no history of VTE receiving adjuvant hormonal therapies; or iii) solely for extending survival when there is no history of VTE.

… and treatment/secondary prophylaxis

For patients with symptomatic cancer-associated thrombosis and those with incidental VTE, LMWHs are recommended for the initial 5–10 days of treatment and ≥6 months for secondary prophylaxis if tolerated (see Table 1b).[23,25,27,28,30–33,36–38] It is usually recommended that anticoagulation be continued until the cancer is cured.[27,32,34,39] Any patient with a massive PE and haemodynamic compromise should be considered for thrombolysis under expert haematological advice and taking into consideration the larger clinical picture of the patient. Although cancer is not an absolute contraindication, often such patients do have contraindications due to their disease and its treatment, and their risk of bleeding is often high. Anticoagulation should be continued in the presence of active malignancy, with the patient's status, bleeding risk and preferences considered. While continuing LMWH is preferred and considered likely to be more effective than VKAs, currently the optimal dosing is not clear and there is little direct supportive evidence. However, it is also worth considering that after 6 months of daily injections, the patient may wish to switch to an orally administered agent. Warfarin

therapy (INR 2–3) can also be considered if long-term LMWH is not feasible, but it should be noted that while VTE recurrence risk in cancer-associated incidental PE is similar with LMWHs and VKAs, the latter have been associated with greater bleeding risk.[40,41]

VTE recurrence is partly treatment-dependent, with a lower rate of 6–9% among patients treated with LMWH compared with 10–17% with warfarin and VKAs.[33,42–46] The CLOT study did not find a significant reduction in fatal PE in the LMWH group – there was predominantly a reduction in recurrent DVT.[43] Increasing the LMWH dose guided by anti-XA level may be considered.[47] Furthermore, LMWH after a cancer-associated thrombosis is not associated with increased risk of bleeding.

While LMWHs and UFH have similar efficacy, the advantages with LMWHs lie in their easier administration, more reliable pharmacokinetic profiles and reduced propensity to cause HIT.[36] There is also evidence that LMWHs are associated with a lower risk of major haemorrhage than UFH.[48] Trial data have provided variable, inconsistent findings for mortality between LMWHs and other anticoagulants; however, most trials have not been powered for this endpoint. A Cochrane review concluded that LMWHs are possibly associated with reduced mortality compared with UFH, but both risk of bias in studies and likelihood of publication bias contribute to the lack of clarity.[49] It has also been suggested that anticoagulants, particularly LMWHs, may have antineoplastic effects through mechanisms such as interference with tumour cell adhesion, invasion, metastasis formation, angiogenesis and the immune system, although clinical validation is required.[50]

DOACs not recommended

While oral dosing may be more convenient, there is limited evidence for oral anticoagulants – clinical trials are ongoing. VTE guidelines that are not specific for patients with cancer may recommend DOACs for some patient groups, but, importantly, there is a paucity of evidence for efficacy and safety in patients with cancer. Due to this lack of evidence, DOACs are not recommended for VTE prophylaxis or treatment in any of the recently published guidelines specific for patients with cancer outside of clinical trials (DOACs were not considered in earlier guidelines due to their relatively recent rise in use). [23–32,36,38] The only exception is the 2015 UK guidance from the British Committee for Standards in Haematology, which includes DOACs in its alternatives, along with warfarin, for treating symptomatic cancer-associated VTE when LMWHs are not tolerated.[33] However, despite a possible perceived patient preference for oral agents among healthcare professionals, data on patient preference for anticoagulation suggest that a greater proportion favour efficacy and safety over convenience of route of administration, and that treating their cancer disease is of greater importance to them than VTE.[51]

Adherence to published guidelines based on good evidence is important to minimise the additional burden of thrombolytic events in already unwell patients with cancer. The main aims are to prevent fatal VTE, recurrent VTE and long-term complications of VTE. A recent audit at Christchurch hospital found that only 11% of the 194 eligible patients admitted to the oncology ward at Christchurch hospital received thromboprophylaxis according to ACCP guidelines.[52]

Other considerations

There are a number of contraindications to anticoagulants (see below).[23] Some can be corrected (e.g. thrombocytopenia – see below) and others are time-dependent (e.g. surgery within 24 hours) meaning that anticoagulant therapy can be delayed. Where prophylactic anticoagulants can never be an option, use of mechanical thromboprophylaxis can help mitigate the risk. When anticoagulants cannot be used therapeutically, IVC insertion is a potential option, although their association with VTE recurrence must be considered, and evidence for their use in this setting is limited.

The consensus is that full anticoagulation poses no excess risk for patients with a platelet count ≥50 × 10^9/L.[25,33] However, for patients with a platelet count <50 × 10^9/L, platelet support should be given so full-dose anticoagulation can subsequently be administered, especially immediately after thrombosis development. Platelet counts of 25–50 × 10^9/L require frequent assessments to determine the safety of anticoagulation for that individual. If the platelet count remains <25 × 10^9/L, full-dose anticoagulation should be avoided. IVC filters should only be inserted if anticoagulants are strongly contraindicated, with removal as soon as anticoagulation is possible; they are not indicated for VTE recurrence alone.

Contraindications to anticoagulant thromboprophylaxis[23]

- Active or high risk of bleeding
- Platelet count <50 × 10^9/L
- Pre-existing coagulopathy
- History of severe gastrointestinal bleeding
- INR >1.3
- Primary brain tumours or brain metastases associated with high likelihood of spontaneous haemorrhage
- Renal dysfunction
- Surgery scheduled in next 24 hours
- Bacterial endocarditis
- Pericarditis
- Severe, uncontrolled malignant hypertension
- Severe head trauma
- Epidural catheter placement
- History of HIT
- High risk of falls

Table 1a. Guideline recommendations for thromboprophylaxis in patients with cancer

Recommendation	Supported by*
Primary prophylaxis	
Medical inpatients (especially with reduced mobility) Mechanical prophylaxis plus LMWH for duration of hospital stay SC enoxaparin 40 mg/day SC dalteparin 5000 U/day SC fondaparinux 2.5 mg/day SC UFH 5000U every 8–12h	ANZWP, ASCO, BCSH, CECR, ESMO, ICPG, ISTH, NCCN, NICE, SEOM
Low-risk surgical inpatients Mechanical prophylaxis plus LMWH as for medical inpatients for 7–10d duration	ANZWP, ASCO, CECR, ESMO, ICPG, NCCN, NICE, SEOM
High-risk surgical inpatients (including abdominal and pelvic surgery) Mechanical prophylaxis plus LMWH as for medical inpatients for 28–35d duration	ANZWP, ASCO, CECR, BCSH, ESMO, ICPG, NCCN, NICE, SEOM
Primary or metastatic brain cancer admitted for neurosurgery LMWH as for medical inpatients for 18–24h postsurgery plus mechanical thromboprophylaxis for duration of hospital stay	ANZWP
Primary or metastatic brain cancer admitted for non-neurosurgical reasons Mechanical prophylaxis plus LMWH as for medical inpatients	ANZWP
Outpatients/ambulatory care setting/chemotherapy None for routine solid tumours – see recommendations for specific anticancer agents	ANZWP, ASCO, BCSH, CECR, ESMO, NCCN
Indwelling venous access devices Thromboprophylaxis not recommended	ANZWP, BCSH, CECR, ICPG
High-risk patients during travel LMWH and graduated compression stockings	ANZWP
Patients receiving thalidomide or lenalidomide ±steroids for multiple myeloma[53] Low risk (lenalidomide and low-dose dexamethasone recipients with no other risk factors): oral aspirin 100 mg/day for ≥6 months Others: SC dalteparin 5000 U/day OR SC enoxaparin 40 mg/day OR warfarin (target INR 2–3) for ≥6 months	ANZWP, ASCO, BCSH, NCCN
VKA (low or therapeutic dose), LMWH (prophylactic dose) or low-dose aspirin	ICPG
Bevacizumab recipients No specific recommendations – commence VTE prophylaxis according to clinical setting during periods of immobilisation	ANZWP
Tamoxifen recipients During periods of immobilisation, consider withholding tamoxifen and starting VTE prophylaxis according to clinical setting	ANZWP

*Guidelines ascribed to a recommendation may not include all the corresponding recommendations or provide the stated regimen details, but in general they are consistent and are not contradictory

Table 1b. Guideline recommendations for treatment/secondary prophylaxis of VTE (including incidental VTE) in patients with cancer

Recommendation	Supported by*
All cancers except brain tumours LMWH for ≥6mo SC enoxaparin 1 mg/kg every 12h or 1.5 mg/kg every 24h SC dalteparin 200 U/kg for 1mo then 150 U/kg OR OR SC fondaparinux every 24h according to bodyweight: 5mg, 7.5mg and 10mg for <50, 50–100 and >100kg, respectively OR IV UFH 80 U/kg bolus followed by continuous infusion starting at 18 U/kg/h and adjusted to maintain APTT 1.5–2.5 times baseline (transition to warfarin [INR 2–3] in proximal superficial thrombophlebitis) DOACS not recommended (& ISTH)	ANZWP, ASCO, BCSH, CECR, ESMO, ISTH, NCCN, SEOM
With low or moderate bleeding risk: extended anticoagulant therapy rather than 3 months of therapy With high bleeding risk: extended anticoagulant therapy LMWH rather than VKA for PE, and VKA rather than DOAC in those not treated with LMWH	ACCP
Brain tumours UFH: – without IV bolus for low-risk VTE – with 40 U/kg bolus for higher risk VTE – 80 U/kg bolus for high-risk if thrombosis risk outweighs bleeding risk Consider IVC filter in patients: – intolerant of anticoagulation for 24h – with recent bleed on noncontrast cranial CT – who have undergone craniotomy with last 3–5 days – with high-risk tumour histology – with contradictions for other anticoagulation	ANZWP
Recurrent VTE If on warfarin, switch to LMWH SC enoxaparin 1 mg/kg every 12h or 1.5 mg/kg every 24h SC dalteparin 100U every 12h or 200U every 24h OR OR SC fondaparinux every 24h according to bodyweight: 5mg, 7.5mg and 10mg for <50, 50–100 and >100kg, respectively If on LMWH, consider increasing dose by 20–25%, based on Xa level If on LMWH or UFH, consider HIT and seek expert haematologist advice Consider IVC filter if anticoagulants contraindicated and risk high (& ISTH) Undertake anatomical evaluation for cause of recurrence	ANZWP, CECR, ESMO
In association with a central venous catheter (initial treatment)/proximal superficial thrombophlebitis (1–3mo) LMWH/fondaparinux as for all cancers (except brain tumours) OR IV UFH as for all cancers (except brain tumours) in central venous catheter-associated DVT Transition to warfarin (INR 2–3) in proximal superficial thrombophlebitis	ANZWP, CECR

*Guidelines ascribed to a recommendation may not include all the corresponding recommendations or provide the stated regimen details, but in general they are consistent and are not contradictory

Table 1c. Details of guidelines for Tables 1a and 1b

ACCP (2012) = American College of Chest Physicians[38]
ANZWP (2012) = Australia and New Zeeland Working Party[23]
ASCO (2014) = American Society of Clinical Oncology[31]
BCSH (2015) = British Committee for Standards in Haematology[33]
CECR (2015) = Canadian Expert Consensus Recommendations[29,30,32]
ESMO (2011) = European Society for Medical Oncology[36]
ICPG (2013) = International Clinical Practice Guidelines (European – Groupe Francophone Thrombose et Cancer, Academic Medical Center, University Medical Center Groningen, French Institute of Cancer)[26]
ISTH (2013–2014) = International Society on Thrombosis and Haemostasis[25,28]
NCCN (2013) = National Comprehensive Cancer Network)[27]
NICE (2010) = NHS National Institute for Health and Clinical Excellence[24]
SEOM (2014) = Spanish Society of Medical Oncology[37]

Key reviews for preventing/ treating cancer-associated thrombosis

Efficacy and safety of anticoagulant therapy for the treatment of acute cancer-associated thrombosis [54]

In 2014, Carrier et al. published a systematic review and meta-analysis of nine RCTs (n=2310) reporting data on recurrent VTE and major bleeding in patients with cancer. Compared with VKAs, LMWHs were associated with a significant reduction in recurrent VTE events (relative risk 0.52 [95% CI 0.36, 0.74]) and no significant difference in major bleeding events (1.06 [0.5, 2.23]), whereas DOACs did not significantly reduce recurrent VTE or major bleeding events (0.66 [0.39, 1.11] and 0.78 [0.42, 1.44], respectively). Data on annualised risks of recurrent VTE and major bleeding in VKA recipients suggested that participants in studies investigating LMWHs had higher risk cancer than those in the DOAC studies.

Treatment of cancer-associated thrombosis[22]

This review by Lee & Peterson discussed what they described were the limited therapeutic options for managing VTE in patients with cancer in 2013. A section on the available anticoagulant choices of LMWH, UFH and fondaparinux noted while there was a paucity of direct comparative studies on these agents in patients with cancer, data extrapolated from subgroup analyses in trials of unselected patients indicated no difference in efficacy between LMWHs and UFH, but LMWHs were associated with a lower 3-month mortality risk, lower costs and simpler dosing. The authors also found good evidence to support the use of long-term LMWHs over VKAs for preventing recurrent VTE. For treating recurrent VTE in patients with cancer, they provide an algorithm that focusses on (after excluding HIT and noncompliance) switching to or increasing the dose of LMWHs. In a section on DOACs, the authors noted concerns regarding extrapolation of published data on these agents from studies in unselected patients to the cancer population.

Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer[49]

This Cochrane review from 2014 analysed data from 16 RCTs investigating anticoagulants in patients with cancer and VTE. In comparisons of LMWHs versus UFH: i) 3-month mortality was reduced (11 trials; risk ratio 0.71 [95% CI 0.52, 0.98]), with little change after excluding studies of lower methodological quality (0.72 [0.52, 1.00]); and ii) no significant difference was evident for VTE recurrence (3 trials; 0.78 [0.29, 2.08]). There was low overall quality of evidence for LMWHs versus UFH due to imprecision and probable publication bias. There was no significant difference between heparin and fondaparinux for mortality, VTE recurrence or major or minor bleeding. One study comparing dalteparin with tinzaparin found no statistically significant mortality difference.

HAEMATOLOGIST'S COMMENTARY

Thrombosis is a well-established complication for patients with cancer, due to both the disease itself and its treatment. Likely causes for this have been discussed in this Educational Series, along with the clinical burden the diagnosis carries. There is now acceptance of both thrombosis risk and that of treatment with anticoagulants. Recognising those at high risk of thrombosis but also those at high risk of bleeding is essential – balancing the two can be difficult.

Many guidelines have been published as summarised in the preceding review. These are evidence based; however, limitations in evidence quality are still a problem. They provide a good framework for treatment decisions; however, they are not a 'one size fits all' solution and it is essential that treatment is individualised to each patient. Even with similar cancers and thromboses, patient factors such as age, comorbidities and disease characteristics (including prognosis) need to be considered. The patient needs to be made aware of the risks, and their preferences also taken into account.

That aside, the advent of the DOACs has changed outpatient VTE treatment. The evidence for their use in patients with cancer is currently scanty – more limited to subgroup analyses of major registration trials. These patients are highly selected and unlikely to reflect a real-world oncology clinic patient. Much needed trials are now underway in patients with cancer, and their results may lead to another option in treatment of VTE in this high-risk population.

ONCOLOGIST'S COMMENTARY

Venous thromboembolic complications of cancer and the treatments of cancer have historically been under-reported in the literature. In recent years this has changed, and there has been a recognition that DVTs and PEs are not only more likely to occur in patients with cancer, but may negatively impact on quality of life, performance status, fitness to undertake anticancer treatments and survival. Increasing research is now being undertaken to develop a clearer understanding of the pathophysiology of VTE and refine VTE prevention and treatment approaches. These treatments will hopefully target appropriate patients with anticoagulants that may be taken orally, require little or no monitoring, carry minimal risks of complications and are effective in reducing VTE events, treating established VTE and reducing morbidity and mortality associated with VTE.

Of particular interest are clinically unsuspected VTEs seen on radiological imaging requested for cancer staging. It is currently recommended that these VTEs are treated in the same way as clinically suspected or symptomatic VTEs; however, this is controversial amongst clinicians, as outcomes from unsuspected VTE with regards to survival are yet to be fully clarified and published data to date have been predominantly retrospective.[55] Prospective research in this challenging area will be important to aid clinicians in treatment decisions.

Potential future directions

While further data from large prospective RCTs specifically in patients with cancer of various types would help to establish the most suitable regimens for VTE prophylaxis and treatment in these populations, particularly on the role of DOACs, at this time LMWHs represent the most suitable anticoagulants to use in most scenarios involving patients with cancer. Genetic testing for VTE risk is another area to watch, as specific mutations in specific cancers may affect VTE risk.

TAKE-HOME MESSAGES:

- Cancer increases risk of VTE
- Cancer-related and unrelated factors can increase risk further
- Patients with cancer should be assessed for VTE risk
- Thromboprophylaxis is recommended for medical and surgical inpatients with cancer
- Guidelines for managing cancer-associated thrombosis are consistent
- LMWHS are recommended for prevention and management of VTE in patients with cancer
- DOACs are not currently recommended in patients with cancer

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