TREATMENT

Patients with cancer are at a greater risk of developing venous thromboembolism than non-cancer patients, partly due to the ability of tumour cells to activate the coagulation system.[1] The incidence of cancer-associated thrombosis (CAT) is further increased by additional risk factors such as chemotherapeutic regimens, surgical procedures, and prolonged immobilisation.[2] Cancer patients who develop venous thromboembolism (VTE) also face much worse outcomes than those with cancer alone. The probability of death for cancer patients with VTE within 183 days of initial hospital admission is over 94% compared to less than 40% for cancer patients without VTE.[3]

The treatment of cancer patients who develop Deep Vein Thrombosis (DVT) or pulmonary embolism (PE) is far more clinically challenging than treating VTE in the non-cancer population as the clinical course of cancer patients is characterised by increased rates of both recurrent thromboembolic episodes and bleeding complications. Based on prospective studies, the annual risk of recurrent VTE is 21-27% and the annual risk of major bleeding is 12-13%.[4,5]

Evidence-based clinical guidelines on the prevention and treatment of CAT have been published in the recent years by several international bodies, including the European Society for Medical Oncology (ESMO),[6] the American Society of Clinical Oncology (ASCO),[7] and the National Comprehensive Cancer Network (NCCN).[8]

Treating CAT patients

CAT treatment requires rapid and accurate risk stratification before haemodynamic decompensation and the development of cardiogenic shock. Anticoagulation is the foundation of therapy. The goal of therapy is to prevent recurrence, extension, and embolism while minimising the risk of bleeding. The aim of VTE treatment can be summarised as follows:

- To prevent fatal PE
- To prevent recurrent VTE
- To prevent long-term VTE and PE complications, such as post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension.

A variety of drugs are available to treat cancer-associated DVT or PE. These include vitamin K antagonists (VKAs), such as warfarin, unfractionated heparin (UFH) and low-molecular-weight heparins (LMWH), including enoxaparin, dalteparin and tinzaparin.

Warfarin is a long-term oral anticoagulant for the prevention and treatment of VTE that is given after initial therapy with LMWH or unfractionated heparin to maintain an international normalised ratio (INR) of 2-3.[9] However, long-term treatment with warfarin in cancer patients has been shown to increase the risk of bleeding and recurrent VTE vs non cancer patients.[4]

Clinical trial data has indicated that INR is suboptimal in the majority of VKA-treated patients with cancer-associated thrombosis due to difficulties maintaining cancer patients in the therapeutic range. For example, in patients receiving oral-anticoagulant therapy in the CLOT trial, the INR was in the therapeutic range for only 46% of the treatment duration (mean 170 days)[19], while it is possible to achieve a time in the therapeutic range (TTR) of more than 70% in specialised anticoagulation clinic for other patients requiring warfarin therapy.[10,11] Consequently, major consensus evidence-based guidelines on CAT, such as NCCN, ESMO and ASCO, recommend LMWHs over VKAs for both the initial and extended treatment.

Due to a wide range of factors, including genetic polymorphism, dietary intake, drug and food interactions, warfarin may be difficult to dose, even in the seemingly uncomplicated patient. The use of warfarin in the oncology patient is complex. As this population may require long-term anticoagulation, warfarin complications could occur due to patient specific factors, drug interactions, chemotherapeutic toxicity, or disease state.[12]

Low-molecular-weight heparins (LMWHs) currently represent the therapeutic agent of choice, as a result of a proven higher efficacy and safety compared to UFH and warfarin. Cancer patients with VTE were twice as likely to develop major bleeding or recurrent VTE after three months treatment with warfarin (21.1%) compared to LWMH (10.5%). In long-term therapy, LMWH was shown to have equivalent efficacy and a superior safety profile compared with initial UFH plus long-term warfarin therapy in patients with proximal deep vein thrombosis. [13] However, as LMWHs require daily subcutaneous injections and weight-adjusted doses, and still confer high risks of recurrent VTE and bleeding complications, management of cancer-associated thrombosis warrants further optimisation.[14] International guidelines on anticoagulation recommend that LMWHs be used for 3–6 months for the treatment of acute VTE in patients with active cancer.[6-8]

Therapeutic options for the management of VTE have expanded with the introduction of Novel Oral Anticoagulants (NOACs), which appear to display a number of advantages compared to conventional anticoagulants in terms of convenient fixed-dose administration and simplicity (no routine monitoring). Several NOACs have been evaluated in clinical trials, based on a comparison largely between NOACs and vitamin K antagonists, and show that NOACs are non-inferior to warfarin in patients without cancer. More recently two of the NOACs have been studied in cancer patients in head to head trials with LMWHs. Both of these studies have shown the NOACs were non inferior to LMWH.[26,27] The rates of VTE were found to be lower in the NOAC group however the incidence of major bleeding was increased. Currently the use of novel oral anticoagulants for either prevention or treatment of VTE in patients with cancer is not recommended by international clinical guidelines.

THROMBOLYTIC THERAPY

Thrombolytic therapy is recommended by NCCN in selected patients, such as those with massive PE who are haemodynamically unstable and without a high risk of bleeding. Patients with massive PE who have contraindications to thrombolytic therapy or who remain unstable after thrombolysis should be considered for catheter or surgical embolectomy.

ASCO guidelines state that the insertion of a vena cava filter is only indicated for patients with contraindications to anticoagulant therapy. It may be considered as an adjunct to anticoagulation in patients with progression of thrombosis (recurrent VTE or extension of existing thrombus) despite optimal therapy with LMWH. For patients with primary central nervous system (CNS) malignancies, ASCO recommends anticoagulation for established VTE as described for other patients with cancer. Careful monitoring is necessary to limit the risk of haemorrhagic complications.

The ESMO guidelines recommend that thrombolytic treatment should be considered for specific subgroups of patients, such as those with PE presenting with severe right ventricular dysfunction, and for patients with massive ilio-femoral thrombosis at risk for limb gangrene, where rapid venous decompression and flow restoration may be desirable.

Extended treatment

Anticoagulation therapy is recommended by ASCO for at least six months for the treatment of patients with cancer with established VTE to prevent recurrence, and, according to the ESMO guidelines, for as long as there is clinical evidence of active malignant disease. The CLOT trial compared the efficacy and safety of immediate LWMH treatment (dalteparin; 200 units/kg daily for 5-7 days) followed by chronic (six months) therapy with an oral anticoagulant agent (coumarin derivative), versus chronic dalteparin therapy (200 units/kg daily for one month followed by 150 units/kg for months two to six) in cancer patients – many of whom had metastatic disease - after diagnosis of acute proximal DVT and/or PE.[19] The probability of recurrent thromboembolism at six months was 17% in the oral-anticoagulant group and 9% in the dalteparin group, and this benefit was achieved without any increase in bleeding.[19] The ESMO guidelines state that the results of this study support the use of LMWHs as chronic anticoagulation therapy in patients with metastatic disease who are diagnosed with acute VTE.

The recent 2015 CATCH trial assessed the efficacy and safety of tinzaparin vs warfarin for the treatment of acute, symptomatic VTE in patients with active cancer.[28] Tinzaparin (175IU/kg) was given once daily for 6 months compared to conventional therapy with Tinzaparin for 5-10 days followed by warfarin, at a dose adjusted to achieve an INR between 2-3 for 6 months. Recurrent VTE occurred in 7.2% of Tinzaparin patients vs 10.5% of those on warfarin (p=0.07). There was no difference in major bleeding however, a significant reduction in clinically relevant non-major bleeding was observed with tinzaparin (p= 0.04).

In a trial comparing long-term therapeutic tinzaparin subcutaneously once daily with usual-care (long-term vitamin K antagonist [VKA] therapy) for three months (outcomes were assessed at 3 months and 12 months), no significant difference was found at 3 months, but the LMWH tinzaparin was shown to be significantly more effective at 12 months than VKA therapy for preventing recurrent VTE in patients with cancer and proximal venous thrombosis.[20]

A study of patients with symptomatic proximal DVT of the lower limbs found that six months treatment with tinzaparin was at least as efficacious and safe as VKA for preventing recurrent VTE, especially in cancer patients. Tinzaparin was also more effective than VKA in achieving re-canalisation of leg thrombi.[21]

In addition, a Cochrane review of anticoagulation for the chronic treatment of VTE in patients with cancer found the incidence of VTE was significantly lower for patients receiving LMWH, compared with oral vitamin K antagonists, along with no significant differences in bleeding, thrombocytopenia, or survival outcomes with use of LMWHs compared with.[22]

ASCO guidelines recommend LMWH for at least six months because of its improved efficacy over VKAs. VKAs are an acceptable alternative for long-term therapy if LMWH is not available. Anticoagulation with LMWH or VKAs beyond the initial six months may be considered for select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy.

The recommended ASCO dosing schedule is as follows:

- Dalteparin - 200 U/kg once daily for 1 month, then 150 U/kg once daily
- Enoxaparin - 1.5 mg/kg once daily; 1 mg/kg once every 12 hours
- Tinzaparin - 175 U/kg once daily
- Warfarin - adjust dose to maintain INR 2 to 3

ESMO guidelines also recommended long-term anticoagulant treatment in cancer patients for six months, stating that 75–80% (ie. 150 U/kg once daily) of the initial dose of LMWH is safe and more effective than treatment with a VKA.

Although the NCCN recommended LMWH as monotherapy (without warfarin) for the first six months of chronic treatment of proximal DVT or PE (and for prevention of recurrent VTE in patients with advanced or metastatic cancer who do not have contraindications to anticoagulation), the decision to continue LMWH beyond this time frame or to switch to warfarin therapy for patients requiring longer durations of anticoagulation therapy should be based on clinical judgment.

RECURRENT VTE

Cancer-associated thrombosis should be considered a chronic disease for which the risk of recurrence persists for many years after the initial event.[23] Research has suggested that many patients with cancer with an initial episode of VTE may require extended, sometimes lifelong, antithrombotic therapy, but the risks of bleeding must be carefully weighed against the thromboprophylaxis benefit associated with treatment.[5]

Cancer patients have a three-fold risk of recurrent VTE and a three- to six-fold risk of major bleeding compared with patients without cancer.[5] If recurrence of VTE in a cancer patient on anticoagulant therapy occurs, the patient should be checked for progression of their malignancy.

ESMO guidelines recommend that patients on long-term anticoagulation with VKA who develop VTE when their INR is in the sub-therapeutic range can be retreated with UFH or LMWH until VKA anticoagulation achieves a stable INR between 2.0 and 3.0.

If VTE recurrence occurs while the INR is in the therapeutic range there are two options: either shift to another method of anticoagulation (UFH or LMWH) or increase the INR (to a target of 3.5). Full-dose LMWH (200 U/kg once daily) can be resumed in patients with a VTE recurrence while receiving a reduced dose of LMWH or VKA anticoagulation as a long-term therapy. Escalating the dose of LMWH results in a second recurrent VTE rate of 9%; it is well tolerated, with few bleeding complications.

The ASCO guideline for recurrent VTE recommends that if the patient is on standard dose of anticoagulant therapy, assess him/her for treatment complications, heparin-induced thrombocytopenia (HIT), and evidence of mechanical compression from malignancy.

CONTRAINDICATIONS TO ANTICOAGULATION

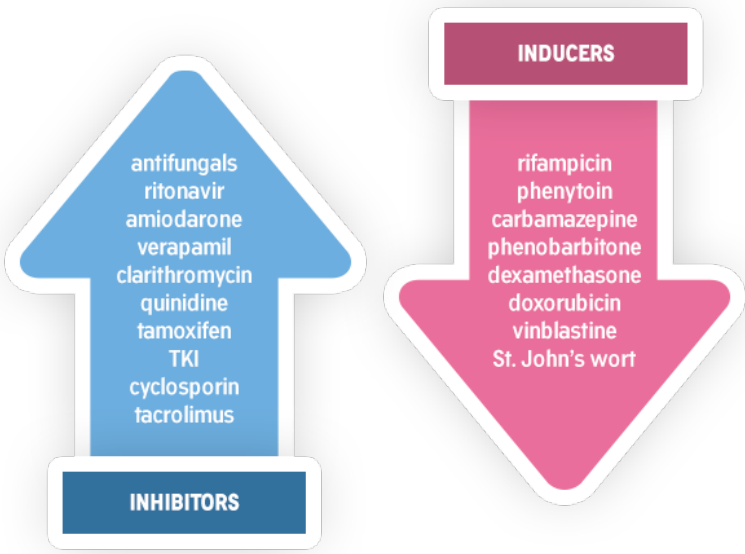
Contraindications to anticoagulation include uncontrollable bleeding, active cerebrovascular haemorrhage, dissecting or cerebral aneurysm, bacterial endocarditis, active peptic or other gastrointestinal ulceration, severe uncontrolled or malignant hypertension, severe head trauma, pregnancy (warfarin), heparin-induced thrombocytopenia and epidural catheter placement. The NCCN advised: "Frequent re-evaluation of these contraindications and the risks and benefits of anticoagulation therapy for any cancer patient considered to be at increased risk for bleeding to facilitate the implementation of this therapy if and when it becomes clinically prudent."

RISKS ASSOCIATED WITH ANTICOAGULATION THERAPY

As previously discussed, the use of anticoagulants in cancer patients is complicated by the fact that these patients have higher risks of both recurrent VTE and bleeding. Other risks associated with chronic use of anticoagulants include osteoporosis and heparin-induced thrombocytopenia (HIT) for patients receiving heparins, and drug and food interactions for patients receiving oral anticoagulants.

NEW ORAL ANTICOAGULANTS

Recently, factor-specific oral anticoagulants were developed that target either activated thrombin (eg. dabigatran etexilate) or activated factor X (factor Xa; eg. rivaroxaban, apixaban or edoxaban). Unlike LMWHs and warfarin, which inhibit multiple coagulation factors, novel oral anticoagulants (NOACs) target specific clotting cascade factors, they do not require laboratory monitoring to achieve therapeutic anticoagulation, they can be taken orally in



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Effect of Inhibitors and Inducers of P-Glycoprotein or CYP-3A4 Pathways on Plasma Levels of Novel Oral Anticoagulants (NOAC). TKI, tyrosine kinase inhibitor [15]

fixed doses, and they have minimal food and drug/drug interactions.

International guidelines do not currently recommend the use of NOACs for treatment of VTE in patients with cancer[7]

The use of NOACs for either prevention or treatment of VTE in patients with cancer is currently not recommended by international consensus guidelines.

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