

Epidemiology and Management of Uncomplicated Thrombosis in Cancer Patients

An overview of the causes of cancer-related thrombosis and options for anticoagulation therapy.

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Thrombosis is a major complication of both cancer and its treatment. In up to 10% to 20% of patients, this can be the presenting sign of cancer, especially in older patients or those with idiopathic thrombosis. Furthermore, up to 25% of patients with spontaneous thrombosis will develop cancer within 2 years. Certain presentations are more worrisome for underlying cancer as the cause (ie, warfarin-refractory thrombosis, idiopathic bilateral deep vein thrombosis [DVT], or both arterial and venous thrombosis), and the most frequently associated cancers are adenocarcinoma of the lung and gastrointestinal tract, especially pancreatic cancer. Primary brain tumors, as well as kidney, ovarian, and uterine cancers, are also associated with a higher risk of thrombosis,¹ but the risk does not appear to be as high for breast and prostate cancer.²

Despite the fact that thrombosis can be an early sign of cancer, studies have not shown the benefit of extensive evaluations (eg, CT) of these patients, and current recommendations include age-appropriate cancer screening (eg, mammograms, colonoscopy) and complete workup in the presence of any worrisome signs, such as guaiac-positive stools.³

A common finding in cancer patients is incidental discovery of pulmonary embolism on a CT scan that was performed for tumor staging or to evaluate the patient's response to chemotherapy. Despite the incidental nature of this discovery, the prognosis is just as threatening as any cancer-related thrombosis, and aggressive treatment with anticoagulation is required.⁴

The etiology of the cancer-related thrombosis is complex, and many factors can potentially play a role.^{5,6} Tumors may directly activate the procoagulant factor VII by tumor-expressed tissue factor. Patients with cancer have elevated inflammatory cytokines that can further

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augment the hypercoagulable state. Cancer treatment can also lead to thrombosis. Surgery in cancer patients increases this risk by threefold compared with similar operations in patients without cancer.⁷

Increasingly, chemotherapy has also been associated with thrombosis. Adjuvant chemotherapy for breast cancer has been associated with an increased risk of both arterial and venous thromboembolism in 5% to 7% of patients.⁸ L-asparaginase, an effective therapy for acute lymphocytic leukemia, is associated with a 5% to 20% incidence of thrombosis in adult patients.^{9,10} The antimyeloma agents thalidomide and lenalidomide are also both associated with thrombosis rates as high as 36% to 75%.¹¹⁻¹³ The incidence is higher with the use of dexamethasone and with chemotherapy, especially doxorubicin. Targeted antineoplastic therapy also increases the risk of thrombosis.¹⁴

Bevacizumab has been associated with an approximate twofold increase in arterial thrombosis,¹⁵ but not venous disease.¹⁶ This may be a class effect of vascular endothelial growth factor inhibition, as vascular endothelial growth factor tyrosine kinase inhibitors, such as sorafenib and sunitinib, also increase the risk of arterial thrombosis by 2.2-fold.¹⁷ Several of the new tyrosine kinase inhibitors developed for treating chronic myelogenous leukemia also increase the risk of arterial thrombosis.¹⁸

TABLE 1. INITIAL TREATMENT OPTIONS FOR CANCER-RELATED THROMBOSIS

Treatment Option	Dosage
LMWH	<ul style="list-style-type: none"> Dalteparin 200 IU/kg daily for 1 month, then 150 IU/kg daily Enoxaparin 1 mg/kg every 12 h or 1.5 mg/kg daily
Direct oral anticoagulants	<ul style="list-style-type: none"> Apixaban 10 mg twice daily for 1 week, then 5 mg twice daily Rivaroxaban 15 mg twice daily for 3 weeks, then 20 mg daily
Warfarin	<ul style="list-style-type: none"> Target international normalized ratio of 2–3: LMWH must be started first and continued for at least 5 days

ANTICOAGULATION THERAPY

Cancer-related thrombosis requires aggressive anticoagulation.^{19,20} Table 1 summarizes the initial treatment options. Initial therapy should be low-molecular-weight heparin (LMWH) for at least 5 days. Five trials have compared treatment with LMWH for 3 to 6 months versus warfarin at an international normalized ratio of 2 to 3.^{21,22} Results have been mixed, with all studies showing that LMWH is just as safe as warfarin and some showing superiority. Most guidelines recommend treating cancer-related thrombosis with LMWH for 6 months; however, in patients who do not tolerate injections or cannot afford LMWH, warfarin or direct oral anticoagulants are reasonable options.²¹ It is unknown if continuing therapy with LMWH after the initial 6 months would have the same possible benefit or if changing back to warfarin/direct oral anticoagulants is best. Patients with tumors at high risk of thrombosis, such as lung or brain cancer, may better be served by continuing LMWH.

There are only limited data for use of direct oral anticoagulants in cancer patients, but they appeared to be both safe and effective in a large meta-analysis.²³ Because many patients do not tolerate injections or cannot afford them, direct oral anticoagulants are a reasonable option because they are easier to use and do not cause food and drug interactions, making them more flexible to use than warfarin. However, more data are needed to determine whether direct oral anticoagulants can supplant LMWH in all patients.

Those with recurrent thrombosis who are on warfarin or direct oral anticoagulants need to be treated indefinitely with LMWH. The rare patient who has recurrent thrombosis despite LMWH therapy may benefit from either increasing the dose by 25% or changing to fondaparinux.²³

TABLE 2. DURATION OF ANTICOAGULATION THERAPY FOR CANCER PATIENTS

Presentation	Duration of Anticoagulation
Metastatic cancer	Indefinitely
Thrombosis after curative surgery	3 months
Thrombosis after curative surgery and receiving adjuvant therapy	1 month after completion of chemotherapy

Despite the concern for intracranial hemorrhage, the presence of brain tumors or brain metastases is not a contraindication to anticoagulation, especially given the high rate of thrombosis in primary brain tumor patients. The only exceptions are brain metastases from thyroid cancer, melanoma, renal cancer, or choriocarcinoma, as these tumor metastases have a high rate of bleeding.²⁴

Duration of Therapy

Table 2 summarizes the duration of anticoagulation therapy for cancer patients. For those with metastatic disease, therapy should continue indefinitely, as the thrombotic stimulus of the tumor is always present. The duration of therapy is less well defined for patients who have undergone curative therapy. For these patients, 3 months of anticoagulation is recommended. For patients who undergo adjuvant chemotherapy after surgery, one approach is to continue anticoagulation for 1 month after completing chemotherapy, based on the concern regarding the prothrombotic effects of chemotherapy.

Use of Anticoagulants in Thrombocytopenic Patients

An issue for which there is little guidance is anticoagulation in patients who are or are at risk of becoming thrombocytopenic.²⁵ For venous thrombosis, full-dose heparin or warfarin can continue as long as the platelet count is more than $50 \times 10^9/L$ and, for prophylactic dosing of LMWH or direct oral anticoagulants, if the platelet count is down to $20 \times 10^9/L$.²⁶

INFERIOR VENA CAVA FILTERS

The use of inferior vena cava (IVC) filters in cancer patients remains contentious. Studies show that cancer patients who undergo IVC filter placement have a higher death rate than those treated with anticoagulation, but these data are confounded by the fact that patients who are ineligible for anticoagulation therapy are sig-

As with pulmonary embolism, cancer patients are often diagnosed while undergoing scanning for other reasons.

nificantly sicker and at a higher risk of death.²² The rate of IVC-related thrombosis in cancer patients is double that of patients without cancer but still occurred in < 5%.²⁷ As seen in other studies, the presence of IVC filters also raises the risk of DVT. The most agreed-upon indication for filter placement is proximal DVT in those who cannot be anticoagulated due to acute bleeding. However, especially in these very hypercoagulable patients, filters cannot replace anticoagulation, which should be initiated as soon as it is feasible.²¹

VENOUS CATHETER THROMBOSIS

Central venous catheters are essential to many aspects of cancer therapy, but the clinically apparent incidence for catheter-related thrombosis is estimated to be 5%. The signs can be nonspecific, and the incidence of thrombosis is thought to be underestimated given the higher incidence reported in screening studies. Patients with catheter-related thrombosis often notice arm pain and swelling. Diagnosis is made by Doppler ultrasonography, but some patients may only have central vein thrombosis, which requires venography or CT angiography to make the diagnosis. As with pulmonary embolism, cancer patients are often diagnosed while undergoing scanning for other reasons.

Therapy is not well defined. For peripherally inserted central catheters, data are increasingly showing that simply removing the catheter may be the safest approach, as the risk of bleeding with anticoagulation is high, and therefore it is best to reserve anticoagulation for the severely symptomatic.²⁸ For thrombosis with tunneled lines, anticoagulation should be administered unless the risk of bleeding is substantial. One trial has shown that the catheter can remain in place with 3 months of anticoagulation.²⁹ Prevention of catheter-related thrombosis is difficult because prophylaxis has not been shown to be beneficial.

SUMMARY

Cancer patients can develop thrombosis for many reasons, and the primary management strategy is aggressive anticoagulation. Future trials will define the role of new agents for cancer-related thrombosis. ■

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