Deep Vein Thrombosis Interventions in Cancer Patients

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Abstract

The presence of cancer increases the risk of deep vein thrombosis (DVT), DVT recurrence, and treatment-related bleeding, and therefore offers distinctive clinical considerations when planning treatment. Anticoagulation with a low-molecular-weight heparin is the preferred initial and long-term therapy in cancer patients. Inferior vena cava filters may be used judiciously for patients with cancer-related DVT who have contraindications to anticoagulation or who exhibit breakthrough pulmonary embolism (PE) despite anticoagulation, but should be removed when the PE risk is felt to subside. Because moderate-quality evidence suggests that the use of catheter-directed thrombolysis (CDT) can prevent the postthrombotic syndrome, cancer patients with acute iliofemoral DVT, low expected bleeding risk, and good functional status may reasonably be considered for CDT if DVT-related sequelae are likely to be a dominant contributor to the patient's clinical condition, functional status, and quality of life. In selected patients who have chronic venous symptoms from mass/nodal compression of the pelvic veins, endovascular stent placement may provide symptom relief. As current recommendations are based on very limited data, further studies would be welcome to better delineate the most appropriate use of endovascular therapies in patients with cancer.

Keywords

- ▶ deep vein thrombosis
- ▶ cancer
- ▶ thrombolysis
- ▶ anticoagulation
- ▶ stent

Objectives: Upon completion of this article, the reader will be able to individualize deep vein thrombosis therapy to the needs of the patient with cancer.

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The treatment of deep venous thrombosis (DVT) in cancer patients requires attention to the unique risk factors and

comorbidities of this complex population. Compared with the general population, cancer patients have a 4.1-fold increased risk of thrombosis, which increases to 6.5-fold when on chemotherapy.¹ As a result, the annual incidence of venous thromboembolism (VTE) in this population is estimated to be 1 in every 200 cancer patients.¹ Cancers of the pancreas, ovary, and brain are the most strongly associated with thrombotic complications.² Aside from increased risk of VTE recurrence, cancer patients are more likely to experience significant adverse events during treatment. Following an acute thrombotic event, patients with cancer have a four- to eightfold increased risk of death compared with a noncancer population.^{3,4}

The acquired thrombophilia of cancer patients is secondary to a complex pathophysiology of tumor cells, which can both activate the clotting cascade and inhibit normal antithrombotic properties.⁵ Additional local factors such as vascular compression and stasis can serve as further inciting factors.

When coupled with chemotherapy, the risk of thrombosis is further increased by agents such as bevacizumab, thalidomide, and lenalidomide, which activate endothelial cells and platelets, and lead to vascular endothelial damage.⁶ Here, we review special considerations for the acute treatment and chronic management of DVT and postthrombotic syndrome (PTS) in this at-risk population.

Anticoagulation

In the acute phase, the National Cancer Care Network (NCCN) guidelines recommend the use of low-molecular-weight heparin (LMWH) for initial therapy. However, if LMWH is not feasible in the long term, unfractionated heparin (UFH) or fondaparinux may be used as a parenteral transition for the first 5 to 7 days until a therapeutic dose of warfarin is achieved.⁷

Following the initial acute phase, both the American College of Chest Physicians (ACCP) and the NCCN guidelines recommend LMWH over either a vitamin K antagonist (VKA) or a novel oral anticoagulant (NOAC) for the first 3 months of treatment following a lower extremity DVT.^{7,8} There is an increased rate of recurrent VTE in cancer patients treated with VKAs compared with LMWH. In particular, a systematic review and meta-analysis of randomized controlled trials assessing rates of recurrent VTE in cancer patients revealed a significant risk reduction (RR 0.52; 95% confidence interval [CI]: 0.36–0.74) for patients on LMWH compared with VKA with a nonsignificant increase in bleeding risk.⁹ Difficulty maintaining patients within the therapeutic range on VKAs may contribute to this increased recurrent VTE risk. Therapeutic VKA use in cancer patients is challenging secondary to the interaction of chemotherapeutic drugs with VKAs and the poor tolerance of many cancer patients to oral medications. Thus, LMWH is a more reliable alternative.

While anticoagulating cancer patients, it is important to be aware of the increased bleeding risk in this subpopulation. During 1 year follow-up, cancer patients had a 2.2 times increased risk of bleeding (95% CI: 1.2–4.1) compared with noncancer patients.¹⁰ Propensity for bleeding was related to cancer severity rather than degree of anticoagulation. Additionally, bleeding was most likely to occur within the first month of anticoagulant treatment.

Despite the increased risk for bleeding complications in cancer patients with VTE, the ACCP does not recommend a scheduled stop date for anticoagulation, even in patients who are considered a high bleeding risk. Furthermore, given the risk for DVT extension, in cancer patients with isolated calf DVT, anticoagulation is favored over surveillance.

Endovascular Therapy Options

For patients with extensive iliofemoral DVT, catheter-directed thrombolysis (CDT) in addition to anticoagulation has been proven to be more effective in reducing the risk of PTS (RR: 0.64, 95% CI: 0.52–0.79) compared with anticoagulation alone.¹¹ However, there is also a significantly increased risk of bleeding complications (RR: 2.23, 95% CI: 1.41–3.52) with

CDT, including fatal or intracranial bleeding. The degree of residual clot following CDT has been correlated with the risk for developing PTS.^{12,13} Given the significant impact of PTS on health-related quality-of-life (QOL) scores,¹⁴ CDT is an important consideration for patients with otherwise few comorbidities and/or QOL issues. However, it should be noted that CDT has not been shown to improve long-term QOL; in the CAVENT randomized clinical trial, there was no difference in health-related QOL at 2 years in patients treated with CDT plus anticoagulation versus anticoagulation alone.¹⁵

Early experiences suggested that cancer patients may be less likely to experience durable benefit from CDT.¹⁶ Since then, cancer patients have been systematically excluded from the majority of large series evaluating the results of CDT for DVT. Higher rates of recurrent VTE have been observed in cancer patients; however, subsequent experience has shown that this extends both to patients who receive, or do not receive, CDT as part of treatment. Still, evidence for the use of CDT in this subpopulation is limited. Survey of the nationwide inpatient sample from 2005 to 2010 for cancer patients with proximal lower extremity and/or caval DVT demonstrated that there was significantly higher morbidity and resource utilization with CDT compared with anticoagulation alone. Additionally, there was a trend toward higher in-hospital mortality.¹⁷ However, of note, this study was not designed to enable assessment of CDT's efficacy, so it provides an incomplete characterization of the procedure's risk-benefit ratio in this population. In fact, a retrospective cohort review comparing CDT for acute DVT in cancer and noncancer cohorts reported similar rates of clot lysis (66.7 vs. 64.6%), major bleeding complications (4.9 vs. 3.4%), and pulmonary embolism (PE) (1.6 vs. 1.7%) in 202 total limbs and concluded that CDT remains equally safe in this special population.¹⁸ Thus, there is no strong evidence to routinely exclude these patients.¹⁹

However, discriminate patient selection remains important. Patients who are most likely to benefit from CDT include those with iliofemoral DVT, symptoms for less than 14 days, good functional status, a life expectancy over 1 year, and a low risk of bleeding. According to SIR guidelines, cancer patients who are undergoing evaluation for CDT based on the aforementioned criteria should undergo evaluation for brain metastases if there is a propensity of their cancer to spread to the central nervous system.²⁰ Additionally, unless there are significant QOL factors or clinical evidence of impending limb-threatening circulatory compromise, CDT for acute DVT may often not be clinically warranted. Instead, in cancer patients with other overwhelming QOL considerations including complex cancer treatment algorithms and/or chronic cancer-related pain, anticoagulation alone is likely the most appropriate therapy.

On the other hand, if a cancer-related DVT is contributing to severe chronic symptoms that are causing functional or QOL impairment, (e.g., compressive nodal mass in pelvis), then more aggressive treatment options such as iliac vein stent placement with or without CDT may be considered for palliative treatment to prevent a further reduction in QOL.²¹

Patients with QOL issues isolated to their DVT are often the best candidates for CDT and other more aggressive treatment options.

Inferior Vena Cava Filters

Inferior vena cava (IVC) filters are best utilized when restricted to patients with acute VTE with contraindications to anticoagulation.¹⁹ In cancer patients treated with IVC filters, recurrence rates of VTE have been reported as high as 32%.²² Given this increased risk of recurrent DVT, IVC filters should be used judiciously in the cancer population, with placement of a retrievable IVC filter for patients who have a significant likelihood of becoming candidates for anticoagulation. For most cancer patients, filter removal should be strongly considered when the IVC filter is no longer needed per Food and Drug Administration guidelines.^{23,24}

Clinical Outcomes

Following initial DVT, the risk of recurrent DVT is higher in cancer patients compared with the general population (hazard ratio [HR]: 10.7, 95% CI: 3.5–32.8).²⁵ Cancer patients have an estimated 15% risk of recurrence per year.^{3,26} The recurrence rate at 5 years has not been estimated given the high cancer mortality by 5 years. In the DACUS study,²⁷ an additional 6 months of anticoagulation was found to reduce the risk of DVT recurrence in patients who had residual DVT on ultrasound imaging following their initial 6 months of anticoagulation. However, this reduction in recurrent VTE risk was lost once anticoagulation had been stopped. Patients who had no residual DVT by 6-month ultrasound had a low risk of DVT recurrence within 1 year (2.9% in 105 patients).

In patients with active cancer, data evaluating the risk for PTS development are limited secondary to poor overall survival in these patients. However, the risk of developing PTS does not appear to be influenced by the cause of DVT (unprovoked or secondary to time-limited reversible risk factor).²⁸ In the general population, PTS develops in approximately 20 to 50% of patients following DVT with significant adverse financial and QOL effects.²⁹ In fact, 2 years post-DVT, the development of PTS remained the primary determinant of health-related QOL scores.³⁰ Given this significant risk of PTS in the cancer population and potentially adverse effects, consideration for aggressive treatment should be given to all DVT patients, including those with cancer. Evaluation and treatment planning should be centered on QOL and the potential for improvement.

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