Diagnosing, Treating, and Preventing Venous Thromboembolism in Patients With Cancer

Normand Blais, MD, FRCPC

Patient Description

Mr. L, a 48-year-old African American with metastatic non-small cell lung cancer, presented to the clinic with complaints of increased dyspnea for the previous 48 hours. Medical history was remarkable for arterial hypertension, coronary atherosclerotic disease successfully treated with percutaneous coronary intervention without stent insertion three years earlier, and left upper-lobe lung adenocarcinoma associated with bilateral lung and multiple liver metastases. Therapy included ramipril, aspirin, and an erythropoiesis-stimulating agent. Mr. L also had been given first-line chemotherapy with carboplatin, paclitaxel, and bevacizumab and recently had completed his third treatment cycle.

Physical examination showed a mildly obese man with no respiratory distress. Vital signs included a pulse of 115 beats per minute, blood pressure of 135/85, a respiratory rate at 24 breaths per minute, temperature of 37.6°C, and oxygen saturation of 82% in ambient air corrected by oxygen supplementation of 2 L per minute with nasal prongs. No central vein catheter or jugular vein distension was present. Heart and lung sounds and the abdominal examination were normal. No extremity swelling or discomfort was noted.

Diagnosing, Treating, and Preventing Venous Thromboembolism in Patients With Cancer

Mr. L was hospitalized because of his decreased peripheral oxygen saturation and started on a therapeutic dose of a low-molecular-weight heparin (LMWH) administered subcutaneously once daily. The erythropoiesis-stimulating agent was discontinued, cardiology was consulted, and a decision was made to maintain concurrent aspirin therapy with the planned course of long-term LMWH therapy. Mr. L was encouraged to become mobile and instructed on self-administration of subcutaneous LMWH. Oxygen saturation resolved to healthy levels after 48 hours of hospital surveillance, and Mr. L was discharged with a long-term prescription of the LMWH. Chemotherapy was continued as planned.

Approaches for the prevention and treatment of venous thromboembolism (VTE) (see Figure 1) in patients with cancer are similar to those used in patients without cancer. Nursing interventions that can help reduce the risk of VTE include encouraging patients to be mobile when possible and encouraging early ambulation of patients after surgery. Nurses should monitor the fluid intake of their patients to prevent dehydration, which can increase blood viscosity. Physical approaches to thromboprophylaxis generally undertaken by nurses include the use of intermittent pneumatic compression devices or graduated compression stockings that can help reduce the risk of VTE, particularly after surgery. Physical measures generally are used in conjunction with pharmacologic thromboprophylaxis and are used alone only in the presence of contraindications to antithrombotic drugs.

Long-Term Prophylaxis

Mr. L was continued on daily LMWH therapy after confirmation that the episode of VTE had resolved. The oncologist planned for a six-month period of anticoagulation with the LMWH and...
additional assessment after that period to determine whether to continue LMWH in the long term or switch to an oral vitamin K antagonist (e.g., warfarin) depending on the overall response of Mr. L's cancer and his tolerance of LMWH. The oncology nurse ensured that Mr. L was comfortable with self-injection and knew how to obtain, store, use, and dispose of his medicine at home. The nurse also made Mr. L aware of the need for hydration, mobility, and the lifestyle measures required to minimize the risk of recurrence. In addition, the nurse involved Mr. L's wife in the discussion, with his consent, to increase knowledge and confidence within the family about how to proceed with treatment.

For patients with deep vein thrombosis and cancer, current guidelines recommend using LMWH for the first three to six months of long-term anticoagulant therapy; treatment should be continued indefinitely until the cancer is resolved (Kearon et al., 2008; Nicolaides et al., 2006). Regimens that have been established in randomized clinical trials to be effective for long-term treatment in patients with cancer are discussed in the Eighth American College of Chest Physicians (ACCP) Guidelines (see Table 1). The recommendations set in the ACCP guidelines are based on specific clinical studies. Lee et al. (2003) found that once-daily treatment with the LMWH dalteparin is associated with a significant 50% reduction in the incidence of recurrent VTE in patients with active cancer versus warfarin. Similar findings have been published with smaller trials using tinzaparin (Hull et al., 2006) and enoxaparin (Deitcher et al., 2006; Meyer et al., 2002).

Simple weight-adjusted dosing regimens, which allow patients or their caregivers to administer LMWHs at home, generally have had good patient acceptance. The acceptability of LMWHs has important implications for patient compliance with therapy and the transfer of inpatients to home-based care. Home treatment and freedom from the inconvenience of regular blood sampling for laboratory monitoring provide clear quality-of-life advantages for patients receiving LMWH over oral anticoagulation with vitamin K antagonists.

Some patients with cancer may receive oral anticoagulant therapy, typically with warfarin, as an alternative to secondary prophylaxis with an LMWH. Warfarin commonly is used in the secondary prevention of VTE in other clinical settings (Hyers et al., 2001). However, warfarin use in patients with cancer can be complicated by drug interactions, malnutrition, vomiting, and liver dysfunction as well as the need for regular laboratory monitoring and dose adjustments (Lee & Levine, 2005). Warfarin use in patients with cancer also is associated with substantial risk of VTE recurrence and bleeding (Gitter, Jaeger, Petterson, Gersh, & Silverstein, 1995; Hutten et al., 2000; Palareti et al., 2000; Prandoni et al., 2002). During oral anticoagulant therapy, patients with cancer have a three-fold higher risk of recurrent VTE and up to a six-fold greater risk of major bleeding compared to patients without cancer (Hutten et al.; Prandoni et al., 2002). The issues associated with warfarin use were indeed a major factor leading to the clinical evaluation and subsequent introduction of heparins and LMWHs in secondary thromboprophylaxis in patients with cancer.

### Venous Thromboembolism in Cancer

The association between VTE and cancer has been recognized for more than a century (Trousseau, 1872). Several factors contribute to the hypercoagulable state that exists in patients with cancer (Prandoni, Falanga, & Piccioli, 2005). Cancer cells appear to activate the clotting system directly and stimulate endothelial cells, platelets, and leukocytes to express procoagulant activity by many mechanisms (e.g., cytokine and angiogenic factor secretion) (Prandoni et al., 2005). In addition, cancer therapies increase the risk of VTE (Geerts et al., 2008; Nicolaides et al., 2006).

VTE remains a major preventable cause of morbidity and death in patients with cancer (Geerts et al., 2008). The case of Mr. L is a common scenario in oncology; although Mr. L’s episode of VTE was resolved successfully, the outcome often is more adverse. VTE risk has been estimated to be more than six times greater in patients with cancer than in patients without cancer (Heit et al., 2000); the condition occurs in 4%–20% of patients with cancer (Khorana, Francis, Culakova, Kuderer, & Lyman, 2007). VTE remains the most common cause of death in patients with cancer besides the disease itself (Agnelli, 1997; Donati, 1994).

### Table 1. Low-Molecular-Weight Heparin (LMWH) Treatment Regimens

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin</td>
<td>200 IU/kg body weight every day for one month; 150 IU/kg every day thereafter</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>175 IU/kg body weight subcutaneous every day</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1.5 mg/kg every day</td>
</tr>
</tbody>
</table>

* Different LMWHs may not be therapeutically interchangeable because they possess unique pharmacologic properties. Therefore, each LMWH should be used according to the administration schedule.

Note. Based on information from Buller et al., 2004; Hull et al., 2006; Kearon et al., 2008; Lee et al., 2003; Meyer et al., 2002; Nicolaides et al., 2006.
The nonfatal outcomes of VTE also are clinically significant and often overlooked. Outcomes include chronic venous ulceration and post-thrombotic venous insufficiency, which can increase the duration of hospitalization and impair the quality of life of patients with cancer (Nicolaides et al., 2006). VTE in patients with cancer also necessitates anticoagulant therapy, which has led to two to six times as many bleeding complications than in patients without cancer (Hutten et al., 2000; Palareti et al., 2000; Prandoni et al., 2002).

Although the link between VTE and cancer is well established, the risks of cancer-associated VTE often are underestimated by oncologists (Kakkar, Levine, Pinedo, Wolff, & Wong, 2003; Kirwan, Nath, Byrne, & McCollum, 2003); therefore, VTE frequently is underdiagnosed and undertreated in patients with cancer (Falanga & Zacharski, 2005).

**Primary Prevention: The Preferred Option**

Although Mr. L was treated successfully for his VTE and received long-term prophylaxis with LMWH therapy, identifying him as a patient at risk for VTE before the episode occurred and providing him with primary prophylaxis would have been ideal. The ACCP and the International Union of Angiology have published comprehensive guidelines on the prevention of VTE that recognize several risk factors, including cancer (Geerts et al., 2008; Kearon et al., 2008; Nicolaides et al., 2006). However, thromboprophylaxis currently is underused, and the levels of morbidity and mortality from cancer-associated thrombosis are significantly high (Kakkar et al., 2003; Kirwan et al., 2003). Nurses should discuss the potential need for thromboprophylaxis with clinicians when planning care regimens for patients with cancer.

**Patients Most at Risk**

Surgery and bed confinement are common risk factors for VTE. Patients with cancer undergoing surgery have more than twice the risk of postoperative deep vein thrombosis and more than three times the risk for fatal pulmonary embolism than patients without cancer undergoing similar procedures (Geerts et al., 2008). As a result, current guidelines recommend routine prophylaxis with unfractionated heparin (UFH) or LMWH appropriate for overall level of risk in patients with cancer who require surgery (Geerts et al.; Nicolaides et al., 2006). The guidelines also recommend that all patients with cancer with an acute illness who are admitted to the hospital should be considered for thromboprophylaxis, particularly if other risk factors for VTE are present and bleeding risk is acceptable (Geerts et al.; Nicolaides et al.). However, the optimal duration of postoperative thromboprophylaxis still is debated. Evidence suggests that prolonging LMWH administration for up to four weeks after surgery reduces the risk of VTE without increasing the risk of postoperative bleeding (Bergqvist et al., 2002; Rasmussen, 2003). Prophylaxis may be continued for up to four weeks after hospital discharge in selected high-risk patients, including those who have had major surgery for cancer or have had VTE previously (Geerts et al.; Nicolaides et al.).

The place of primary prevention of VTE in patients with cancer outside the surgery or bed confinement settings is unclear. Identifying patients who are at increased risk for VTE currently is difficult. The presence of asymptomatic deep vein thrombosis is strongly correlated with the subsequent development of symptomatic VTE (Ibrahim et al., 2002; Mismetti, Laporte, Darmon, Buchmuller, & Decousus, 2001), but routine screening of patients was neither effective nor cost effective in preventing clinically relevant VTE because early symptoms are unreliable and sometimes absent (Geerts et al., 2008). In addition, the first symptom of VTE can be sudden death from a massive pulmonary embolism. Little data exist on primary VTE prophylaxis in ambulatory patients with cancer, so additional research is needed.

Although nonsurgical cancer therapies have been shown to increase VTE risk, data to support the use of routine thromboprophylaxis in patients with cancer receiving these treatments currently are lacking (Geerts et al., 2008; Nicolaides et al., 2006). Although having a central venous catheter is recognized as a risk factor for upper-extremity deep vein thrombosis, thromboprophylaxis is not recommended in patients with cancer with the catheters (Geerts et al.; Nicolaides et al.). The incidence of VTE is increased in patients with cancer with central venous catheters, and early studies have suggested benefit for prophylaxis with either low-dose LMWH or warfarin dosed at 1 mg daily. However, randomized trials conducted to date have not confirmed the early results and do not support the premise that the preventive strategies are useful in reducing thrombotic risks in patients with cancer (Bern et al., 1990; Couban et al., 2005; Heaton, Han, & Inder, 2002; Karthaus et al., 2006; Monreal et al., 1996; Verso & Agnelli, 2003).

VTE risks also may vary depending on malignancy type because some studies have shown differential risks among patients with specific types of cancer (Khorana, Kuderer, Culakova, Lyman, & Francis, 2008; Lee & Levine, 2003; Thodi-yil & Kakkar, 2002). Particularly high rates of VTE have been associated with cancers of the brain, ovary, pancreas, stomach, lung, prostate, and kidney, as well as with hematologic malignancies (Stein et al., 2006). As a patient with lung cancer, Mr. L would be considered to have potentially increased risk of VTE.

A number of other independent risk factors may exist in patients with cancer, increasing VTE risk (see Figure 2). In addition, cancer treatments themselves can increase the risk; chemotherapy has been associated with high incidences of VTE in various cancer types (Otten et al., 2002). Thrombotic risks in patients with cancer increase with age, type and stage of cancer, presence of a central venous catheter, prior VTE, surgery or bed confinement settings, and obesity (Bern et al., 2000; Palareti et al., 2000; Prandoni et al., 2000; Rasmussen, 2003). The prevalence of asymptomatic VTE is higher in patients with cancer receiving these treatments currently are lacking (Geerts et al., 2008; Nicolaides et al., 2006). Although having a central venous catheter is recognized as a risk factor for upper-extremity deep vein thrombosis, thromboprophylaxis

---

**Figure 2. Factors That Increase Venous Thromboembolism Risk in Patients With Cancer**

**Note.** Based on information from Geerts et al., 2008.
al., 2004). Hormonal therapies, such as tamoxifen, also were shown to increase VTE risk among women with breast cancer (Deitcher & Gomes, 2004; Fisher et al., 2005). The risk is further increased when tamoxifen is combined with chemotherapy (Pritchard et al., 1996). Antiangiogenic agents are receiving attention as anticancer therapies. Thalidomide, an anticancer treatment that has shown significant activity in multiple myeloma, is being investigated for use in other types of malignancy (Eleutherakis-Papakoulov et al. and up to 30% of patients with multiple myeloma treated with thalidomide and chemotherapy (Zangari et al., 2004). Bevacizumab, a monoclonal antibody to the ligand of the vascular endothelial growth factor receptor, has been associated with arterial thrombotic events, but a meta-analysis of published clinical trials randomizing bevacizumab to placebo could not find an association between bevacizumab and VTE events (Scappaticci et al., 2007). Erythropoietins, which are used to treat anemia in patients with cancer receiving chemotherapy, also are associated with an increased risk of VTE (Bohlius et al., 2006). Indwelling central venous catheters, which often are required in patients with cancer for administration of chemotherapy or for blood sampling, add to the risk of VTE (Bona, 1999).

Unfractionated Heparin Versus Low-Molecular-Weight Heparin

Patients may receive either UFH or an LMWH. UFH usually is the least expensive option in terms of initial drug cost, and many centers still use the treatment. However, meta-analyses of randomized trials evaluating the efficacy of initial treatment with LMWHs have shown that LMWHs are just as effective as UFH in preventing recurrent VTE and have improved safety in terms of major bleeding events (Segal, Streiff, Hofmann, Thornton, & Bass, 2007; van Dongen, van Den Belt, Prins, & Lensing, 2004). A lower mortality rate has been suggested for patients receiving LMWH compared to UFH, with the survival benefit potentially accounted for by patients with cancer (Buller et al., 2004; Dolovich, Ginsberg, Douketis, Holbrook, & Cheah, 2000; Gould, Dembitzer, Doyle, Hastie, & Garber, 1999; van Den Belt et al., 2000).

LMWHs have several practical advantages over UFH that largely relate to their longer half-life and more predictable anticoagulant effect. UFH is administered mostly by continuous IV infusion, and frequent monitoring of coagulation status and dose adjustments are necessary because of the unpredictable dose response. However, LMWHs can be injected subcutaneously as weight-adjusted doses twice or even once daily, laboratory monitoring is not required, and treatment can be administered at home rather than in a hospital (Agno et al., 2005; Koopman et al., 1996; Wells et al., 1998). The risk of heparin-induced thrombocytopenia is reduced with LMWH compared to UFH (Warkentin et al., 1995). Nurses are crucial in educating patients about the role of therapy, possible complications, and injection techniques.

Ongoing Research

Research into anticoagulation for patients with cancer is continuing. In addition to the future potential of novel oral drugs, some evidence suggests that LMWHs may increase survival in patients with cancer by a mechanism that may not be directly related to their anticoagulant effects (Altinbas et al., 2004; Kakkar et al., 2004; Klerk et al., 2005; Lee et al., 2005). LMWHs may alter the natural history of early-stage cancers in particular (Altinbas et al.; Kakkar et al., 2004; Lee et al., 2005), suggesting that LMWHs may help prevent dissemination of cancer before the occurrence of metastases. Large multi-institutional clinical trials are planned to help to define the potential roles of LMWHs as direct anticancer agents.

Nursing Implications

Nurses caring for patients with cancer are in a pivotal position to identify patients at risk for VTE, detect signs and symptoms, and implement preventive or therapeutic regimens. In addition to participating with other clinicians in the planning of care and patient management, nurses have a role in educating patients and caregivers about the importance of pharmacologic and nonpharmacologic measures, therefore helping to ensure patient adherence and improve outcomes. Nurses also are well-placed to discuss the risk factors for VTE with patients, encourage self-help measures (e.g., adequate fluid intake, patient mobilization), and advise on the practicalities of self-administration for patients receiving LMWH therapy. By keeping up to date with developments in this crucial area of research, nurses can reduce the burden of preventable morbidity and mortality caused by VTE in patients with cancer.

Author Contact: Normand Blais, MD, FRCPC, can be reached at n.blaiss@umontreal.ca, with copy to editor at CJONEditor@ons.org.

References


