Cancer-Associated Thrombosis

Improving patient adherence to low-molecular-weight heparin therapy

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Cancer-associated thrombosis (CAT) refers to all thrombotic events encountered during the cancer journey. The association of cancer and venous thromboembolism, including deep vein thrombosis and pulmonary embolism, has been widely acknowledged since the 19th century and was first described by Armand Trousseau (1865). The risk for venous thromboembolism is four- to sevenfold higher in patients with cancer (Stein et al., 2006), which can be attributed to several factors, including the prothrombotic nature of the malignancy, administration of chemotherapy, suppression of fibrinolytic activity, use of vascular access devices, and surgical interventions used to treat cancer (Grier, 2014). The incidence of CAT has been rising because of greater chemotherapy use and extended survival time related to advances in cancer treatment (Khorana, Francis, Culakova, Kuderer, & Lyman, 2007a). Although CAT is linked to poorer prognoses and is the second leading cause of death in patients with cancer after disease progression, patients, particularly those receiving chemotherapy, usually have little knowledge or warning of their risk for CAT at the time of diagnosis (Noble, Prout, & Nelson, 2015). The diagnosis of CAT is very physically and emotionally distressing for patients, particularly in the context of the major life event of a recent cancer diagnosis and ongoing cancer treatment. In addition, the management of CAT seems more complicated in the oncology setting because of the lack of ownership of its management among oncologists, primary care physicians, and hematologists.

As patient advocates and educators, oncology nurses should proactively learn about newer developments in the management of CAT and apply that knowledge to daily patient care to ensure the best possible outcomes. This article provides an overview of the most recent standard treatment guidelines for CAT, as well as nursing interventions that may improve patient adherence to and satisfaction with recommended treatment.

Low-Molecular-Weight Heparin Therapy and Its Challenges
In the early 2000s, venous thromboembolism was treated with low-molecular-weight heparin (LMWH) or unfractionated heparin, as well as long-term oral anticoagulants, such as vitamin K antagonists like warfarin (Coumadin®) (Barbosa, 2014). Since 2006, more evidence has shown support for long-term LMWH as first-line treatment for CAT (Akl et al., 2008). Noble et al. (2008) published a comprehensive review of 19 publications, including a meta-analysis of four randomized, controlled trials, of anticoagulation treatment in patients with cancer. The data revealed a 50% reduction in relative risk in recurrent venous thromboembolism without increased bleeding rates in favor of LMWH over a
vitamin K antagonists. The recommendation of long-term LMWH monotherapy was also considered appropriate in the advanced-cancer setting because 47%–65% of the patients enrolled in those trials had metastatic disease. In addition to improved efficacy, LMWH provides other advantages over vitamin K antagonists, including minimal need for monitoring, limited drug interactions, no food interactions, and consistent absorption of the drug owing to its parenteral administration (Lee & Peterson, 2013).

Three LMWHs are widely used in the United States and Canada: dalteparin (Fragmin®), enoxaparin (Lovenox®), and tinzaparin (Innohep®) (Merli & Groce, 2010). Guidelines recommend LMWH over vitamin K antagonists for the treatment of patients with cancer (Barbosa, 2014; Kearon et al., 2012; Lyman et al., 2007; Mandalà, Falanga, & Roila, 2011; National Comprehensive Cancer Network, 2013) and suggest that LMWH treatment last for three to six months. An indefinite course of treatment should be considered for patients on palliative chemotherapy and for those who are in remission but have a very high risk for recurrence (Barbosa, 2014). Because the treatment journey for CAT is prolonged, providers need to be attentive to patient compliance.

Although evidence-based treatment guidelines recommend LMWH monotherapy for CAT, warfarin-based treatment is used more often (Delate et al., 2012; Imberti et al., 2008; Wittkowsky, 2006). Kleinjan, Hutten, Di Nisio, Büllier, and Kamphuisen (2014) presented a similar review and reached similar conclusions: 14% of patients with cancer and pulmonary embolism received LMWH for a prolonged period of time, revealing the need for better adherence to treatment guidelines for venous thromboembolism. The current author observed that clinicians sometimes prescribe oral anticoagulants instead of LMWH based on patient preference. Many patients with cancer prefer to take oral anticoagulants to avoid daily heparin injections, particularly with the emerging use of direct-acting oral anticoagulants to treat venous thromboembolism in patients without cancer. However, the efficacy and safety of direct-acting oral anticoagulants versus LMWH in oncology settings are still unknown (Posch, Königsbrügge, Zielinski, Pabinger, & Ay, 2015).

Seaman, Nelson, and Noble (2014) conducted a qualitative study in a palliative care setting and found that, although LMWH is considered an acceptable intervention, its long-term use is associated with bruising and deterioration at injection sites. Participants favored an oral anticoagulant if it was equivalent to LMWH in efficacy and safety.

**Extensive Pretreatment Education**

The key to successful implementation of nursing interventions and patient adherence to recommendations is adequate education. Patients and their families are far more likely to adhere to prescribed therapy if they understand the rationale behind it. Also, to effect better patient outcomes, oncology nurses should actively integrate the newest knowledge into daily practice. Clinical research shows that LMWH treatment may have an antineoplastic effect (Kuderer, Ortel, & Francis, 2009). The mechanisms by which LMWHs have this effect still need to be elucidated, but their antitumor action likely involves the inhibition of angiogenesis, inhibition of the release of coagulation proteases, immunomodulatory actions, and apoptosis (Khorana, 2007).

Well-written patient education should include the pathophysiology of and patient risk factors for CAT, benefits of LMWH treatment in oncology settings, and the monitoring and safety of LMWH injections (see Figure 1 for an example).

**Improving Patient Experiences of Self-Injection**

Patient refusal of self-injection could prompt physicians to prescribe warfarin-based therapy, although they are well aware of the treatment guidelines (Delate et al., 2012; Imberti et al., 2008; Wittkowsky, 2006). Kleinjan, Hutten, Di Nisio, Büllier, and Kamphuisen (2014) presented a similar review and reached similar conclusions: 14% of patients with cancer and pulmonary embolism received LMWH for a prolonged period of time, revealing the need for better adherence to treatment guidelines for venous thromboembolism.

**FIGURE 1. PATIENT EDUCATION ON LMWH THERAPY**

**PATHOPHYSIOLOGY AND DEVELOPMENT OF RISK FACTORS FOR THROMBOSIS**
- Hypercoagulable state induced by tumor cells
- Surgery
- Immobilization
- Presence of an indwelling central catheter
- Chemotherapy
- New molecular targeted therapies
- Other comorbidities may also influence thrombotic complications
- Novel risk factors: platelet, leukocyte counts, and tissue factor

**BENEFITS OF LMWH IN ONCOLOGY**
- More effective than therapy with vitamin K antagonists
- A retrospective analysis of clinical trials suggested a survival advantage of the LMWH treatment groups (possible antineoplastic properties of LMWH).
- No need for laboratory monitoring of anticoagulant activity
- A shorter half-life that facilitates a temporary interruption for invasive procedures or thrombocytopenia
- Limited drug interactions
- No food interactions or reliance on oral intake or gastrointestinal tract absorption

**MONITORING AND SAFETY OF LMWH**
- Specific patient conditions that may warrant an anti–factor Xa laboratory test
  - Obesity (body mass index greater than 50 kg/m²)
  - Lower body weight (lower than 50 kg)
  - Impaired renal function (creatinine clearance less than 30 ml/minute)
  - Pregnancy
- Awareness of increased risk for bleeding
  - Bleeding monitoring
  - Bleeding management

LMWH—low-molecular-weight heparin

Note. Based on information from Alfano et al., 2004; Altinbas et al., 2004; Babin et al., 2017; Debergh et al., 2010; Elyaman et al., 2014; Kakkar et al., 2004; Klerk et al., 2009; Lee & Peterson, 2013; Lee et al., 2005; Loynes et al., 2002; Moua & Petersen, 2009.
Pain, lumps, and bruising are common side effects of self-injection, making it difficult for patients to locate new areas for injection. As patient educators, nurses play an extremely important role in managing the quality of patient experiences with self-injection of LMWH. Whether their CAT is managed by the oncology team or the primary care provider, patients need face-to-face teaching by nurses. An informative, accurate, easy-to-understand handout is a critical component of patient education on the self-injection of LMWH. Handouts should include detailed step-by-step instructions with illustrations.

The application of adaptive techniques to optimize ongoing injection and reduce patient injury, fear, and anxiety is one of the tasks of oncology nurses. Kuzu and Ucar (2001) investigated the effects of ice application on bruising, hematoma, and pain at the injection site of subcutaneous enoxaparin in patients. Hematoma did not occur at the injection site of any participants, and no significant difference in the incidence or size of bruise among the groups was observed; however, the participants’ perception of pain was significantly less with ice application. Dehghani, Najari, and Dehghani (2014) reported that the duration of enoxaparin injections had no effect on the size of the bruise in patients with acute coronary syndrome. Amaniyan, Varaei, Vaismoradi, Haghani, and Sieloff (2016) found that the local application of cold/hot packs was more effective in reducing bruises following enoxaparin sodium injections compared to local cold-pack application alone. More studies are needed to improve patients’ satisfaction with daily LMWH injections.

**Conclusion**

As many as 20% of adults with malignancy will develop CAT during the course of their disease (Brose & Lee, 2008). In addition to acute and long-term morbidity, CAT remains the number one cause of death during chemotherapy and the second most common cause of all cancer deaths (Khorana et al., 2007b). Although low-molecular-weight heparin improve the outcome of patients with operable non-small cell lung cancer? An urgent call for research. Chest, 126, 601–607. doi:10.1378/chest.126.2.601


