Prophylaxis and Treatment of Venous Thromboembolism in Cancer Patients
A Review

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Abstract: Thromboprophylaxis is underused in patients with cancer, despite the fact that malignancy is a serious risk factor for venous thromboembolism in this population. Major medical guidelines, including those published recently by the American College of Chest Physicians, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network, recommend routine thromboprophylaxis for patients with cancer under certain situations. This review describes current recommendations for primary and secondary prophylaxis in patients with cancer.

Key Words: cancer, venous thromboembolism, prophylaxis, treatment
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Only 59% of surgical patients at risk for venous thromboembolism (VTE) received prophylaxis in a 2006–2007 study, involving more than 68,000 patients at 358 hospitals. It is not surprising, then, that prophylaxis is also underused in patients who develop cancer. 1-6 a well-documented risk factor for VTE (Fig. 1).7,8 Despite the many randomized clinical studies that have demonstrated the effectiveness of primary prophylaxis for reducing VTE and preventing fatal pulmonary embolism (PE) in patients with cancer,9,10 Factors contributing to the underutilization of thromboprophylaxis in patients with cancer include underrecognition of prevalent risk factors, concern over the risk of bleeding, and lack of awareness of thromboprophylaxis guidelines within the oncology community. 11 The Fundamental Research in Oncology and Thrombosis survey was distributed to clinicians worldwide who were involved in cancer care. 12 When results from approximately 4000 completed questionnaires were analyzed, researchers discovered that only about half (52%) of respondents would routinely use thromboprophylaxis for surgical oncology patients. Medical oncology patients fared even worse; respondents considered thromboprophylaxis in only 5% of these patients. When patients with cancer do receive thromboprophylaxis, less than half receive treatment considered in accordance with the American College of Chest Physicians (ACCP) guidelines. 12

Other recent studies have also compared prophylaxis rates in various high-risk patient populations, including patients with cancer. A records review of 20 Oklahoma hospitals revealed that prophylaxis was used in 38% of 419 Medicare patients aged 65 and older who underwent major abdominohiatal surgery. The use of thromboprophylaxis did not increase in the 250 patients considered at highest risk for VTE; only 97 (39%) of these patients received any form of prophylaxis. Of the 97 high-risk patients who did receive prophylaxis, only 64 (66%) received appropriate prophylaxis. Prophylaxis for VTE was also evaluated via the records of medical patients from 2 Canadian hospitals; thromboprophylaxis was used in 38% of cases. 5 In a study of patients who had ultrasound-confirmed deep vein thrombosis (DVT), only 42% of those who had DVT diagnosed during the hospital stay had received thromboprophylaxis within the 30 days immediately prior to diagnosis. 6 This was a very large study involving a prospective registry of 2892 women and 2559 men from 183 US sites. Of these patients, 32% had cancer; other frequently occurring comorbidities included hypertension (50%), surgery within 3 months (38%), immobility within 30 days (34%), and obesity (27%).

Risk of Bleeding
A risk-benefit analysis is critical when determining whether to administer thromboprophylaxis to patients, but a review of adverse events in patients undergoing general surgery shows that the incidence of bleeding related to pharmacologic prophylaxis is typically low. 13 Researchers reviewed 52 randomized controlled trials that evaluated pharmacologic thromboprophylaxis and subsequent bleeding complications in 33,813 patients undergoing general surgery. The most frequent bleeding adverse events were injection-site bruising (6.9%), wound hematoma (5.7%), and drain-site bleeding (2.0%). Major bleeding complications were infrequent; they included gastrointestinal tract (0.2%) or retroperitoneal (<0.1%) bleeding. Bleeding requiring a change in care occurred in less than 3% of cases, and prophylaxis was discontinued in 2% of patients. Surgical intervention was rarely required (<1% of patients). Bleeding complications requiring discontinuation of prophylaxis occurred in 3% of the patients.

Several studies have confirmed a low risk of major bleeding in patients with cancer who receive prophylaxis with low-molecular-weight heparin (LMWH), with no difference in risk of major bleeding noted between LMWH and unfractionated heparin (UFH) in those studies that performed direct comparisons of these treatment options. In the Enoxaparin and Cancer (ENOXACAN) II study, a double-blind, multicenter, randomized trial, patients undergoing planned curative surgery for abdominal or pelvic cancer received enoxaparin for 6 to 10 days followed by either enoxaparin or placebo for an additional 21 days. 14 No statistically significant differences in bleeding events or other complications occurred during the 21-day extended treatment or the follow-up period. The Canadian Colorectal Surgery DVT Prophylaxis Trial also compared enoxaparin with UFH in patients with cancer; the rates of major bleeding and reoperation for bleeding were not significantly different between the 2 treatment groups. 15 The PEGASUS trial compared fondaparinux with dalteparin in patients undergoing abdominal surgery, including 1408 patients with cancer. 16 Rates of major bleeding in this cancer subgroup were low and comparable between the 2 treatments. The Fragmin After Major Abdominal Surgery study evaluated extended prophylaxis with dalteparin in surgical cancer patients. 18 Bleeding events were not increased with 4-week compared with
1-week thromboprophylaxis. Leonardi et al reviewed 26 clinical trials that evaluated DVT prophylaxis in 7639 cancer patients undergoing surgery.19 Bleeding complications required discontinuation of prophylaxis in 3% of patients, but no differences in bleeding complications were noted between patients treated with LMWH and those treated with UFH.

**When and to Whom Should Prophylaxis Be Given?**

Three major sets of medical guidelines recommend routine thromboprophylaxis for patients with cancer under certain situations. Geerts et al, in a 2008 publication, summarize the ACCP evidence-based recommendations for prophylaxis for VTE in a wide variety of conditions, including cancer.9 Routine thromboprophylaxis is recommended for patients with cancer undergoing surgical procedures and patients with cancer who are bedridden with an acute medical illness. The types of recommended prophylaxis are the same as those recommended for patients without cancer who are undergoing similar surgery or who are considered high-risk medical patients. More detail is given in the next section of this article. Routine thromboprophylaxis is not recommended for cancer patients receiving chemotherapy or hormonal therapy, or any patient with cancer when the primary purpose is to improve survival.

The National Comprehensive Cancer Network (NCCN) guidelines consider all adult hospitalized patients with a diagnosis or clinical suspicion of cancer to be at-risk population for the development of VTE.20 If patients have no relative contraindication to anticoagulation treatment, they should be considered for initial prophylactic therapy, with mechanical prophylaxis considered for those who have contraindications for pharmacologic prophylaxis. Options for mechanical prophylaxis include graduated compression stockings and/or intermittent pneumatic compression.9,20

The American Society of Clinical Oncology (ASCO) VTE Guideline Panel recommends that all hospitalized cancer patients and cancer patients undergoing major surgery for malignant disease should be considered for VTE prophylaxis with anticoagulants in the absence of bleeding or other contraindications.13 Routine prophylaxis of ambulatory cancer patients with anticoagulation is not recommended, however, with the exception of patients receiving thalidomide or lenalidomide. The ASCO guidelines state that “the impact of anticoagulants on cancer patient survival requires additional study and cannot be recommended at present.”

Options for prophylaxis include both pharmacologic and mechanical approaches (Table 1). Recommended drugs include low-dose unfractionated heparin, LMWH, and Factor Xa inhibitor.9,11,20 ACCP guidelines cite strong evidence that low-dose unfractionated heparin and LMWH reduce the risk of VTE (both DVT and fatal PE) in patients with cancer who have undergone cancer surgery and specify that “clinicians follow manufacturer suggested dosing guidelines” when using these medications.9 When anticoagulation is contraindicated, recommended mechanical approaches include intermittent pneumatic compression and properly fitted graduated compression stockings.

A patient with a central venous catheter has an additional risk for developing VTE,20 but the benefit of prophylactic therapy has not been proven. There have been no studies that have reported the true incidence of upper extremity DVT and PE in this patient population. The ACCP and ASCO guidelines do not recommend routine mechanical thromboprophylaxis in patients with cancer and central venous catheters unless additional risk factors are present.9,20

Unfortunately, evidence from clinical trials is insufficient to adequately address the issue of duration of VTE prophylaxis. The ACCP and ASCO guidelines describe recent evidence that prolonging the duration of prophylaxis in surgical patients for up to 4 weeks after surgery may provide additional risk reduction. In 2 studies, VTE rates were halved in patients receiving 4 weeks versus 1 week of prophylaxis.9,20 ASCO guidelines state that “there is no evidence to suggest that extending prophylaxis beyond 4 weeks after surgery is beneficial.”9,20

**TABLE 1. Summary of Key Guidelines for Pharmacologic and Mechanical Prophylaxis of VTE**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Pharmacologic</th>
<th>Mechanical</th>
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<tbody>
<tr>
<td>ASCO11</td>
<td>UFH</td>
<td>IPC</td>
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<tr>
<td></td>
<td>LMWH</td>
<td>GCS</td>
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<tr>
<td></td>
<td>Factor Xa inhibitor</td>
<td></td>
</tr>
<tr>
<td>ACCP9</td>
<td>UFH tid</td>
<td>IPC</td>
</tr>
<tr>
<td></td>
<td>LMWH</td>
<td>GCS</td>
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<tr>
<td></td>
<td>Factor Xa inhibitor</td>
<td></td>
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<td>UFH tid</td>
<td>IPC</td>
</tr>
<tr>
<td></td>
<td>LMWH</td>
<td>GCS</td>
</tr>
<tr>
<td></td>
<td>Factor Xa inhibitor (Grade 1A)</td>
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</tbody>
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VTE indicates venous thromboembolism; ASCO, American Society of Clinical Oncology; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; IPC, intermittent pneumatic compression; GCS, graduated compression stockings; ACCP, American College of Chest Physicians; tid, 3 times daily; NCCN, National Comprehensive Cancer Network.
especially in high-risk abdominal or pelvic cancer surgery patients. Extended VTE prophylaxis has improved survival in patients with cancer in some recent clinical trials, and this is discussed in more detail in the accompanying article by DeLoughery.

**TREATMENT OF VTE**

Treatment for venous thromboembolic disease is part of the ACCP Evidence-Based Clinical Practice Guidelines (8th Edition). A paradigm shift has occurred, however, in the type of treatment now recommended for acute VTE in cancer patients, with the publication of data showing lower rates of recurrent VTE with the use of LMWH versus warfarin (Table 2). In a randomized, open-label, multicenter control study published by Meyer et al, subcutaneous enoxaparin sodium (1.5 mg/kg once a day) was compared with warfarin in 146 patients with cancer and VTE. Fewer patients experienced a combined outcome event (defined as recurrent VTE or major hemorrhage within 3 months) in the group of 67 evaluable patients receiving enoxaparin versus the 71 assigned to receive warfarin (10.5% versus 21.1%, \( P = 0.09 \)). Enoxaparin was more effective than warfarin when time to primary outcome was analyzed (Fig. 2). No patient deaths due to hemorrhage occurred in the LMWH group compared with 6 in the warfarin group. The authors concluded that prolonged treatment with LMWH for VTE appeared to be as effective as warfarin in cancer patients but, yet safer.

In a second study, comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy (CLOT), 676 patients with cancer and acute, symptomatic DVT, PE, or both were randomly assigned to subcutaneous dalteparin (once daily for 5–7 days), plus a coumarin derivative for 6 months or dalteparin monotherapy for 6 months. A total of 48 clinical centers in 8 countries participated in this trial. VTE recurred in 27 of 336 patients receiving dalteparin versus 53 of 336 in the coumarin group (hazard ratio, 0.48; \( P = 0.002 \) (Fig. 3). The 2 groups did not differ in the rate of major bleeding (6% and 4%, respectively) (Table 2) or any bleeding (14% and 19%, respectively). Mortality rates were also similar in the

**TABLE 2. Warfarin Versus LMWH for Long-Term Prevention of Recurrent VTE in Patients With Cancer**

<table>
<thead>
<tr>
<th>Study Author</th>
<th>Patients (N)</th>
<th>Drug</th>
<th>DVT Rate While on Warfarin (Patients [%])</th>
<th>DVT Rate While on LMWH (Patients [%])</th>
<th>Bleeding While on Warfarin (Patients [%])</th>
<th>Bleeding While on LMWH (Patients [%])</th>
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</thead>
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<tr>
<td>Meyer</td>
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<td>Enoxaparin</td>
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<td>3</td>
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<tr>
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<td>676</td>
<td>Dalteparin</td>
<td>16</td>
<td>8</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Hull</td>
<td>200</td>
<td>Tinzaparin</td>
<td>10</td>
<td>6</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

LMWH indicates low-molecular-weight heparin; VTE, venous thromboembolism; DVT, deep venous thrombosis; RR, relative risk; CI, confidence interval.

**FIGURE 2. Recurrent VTE or major hemorrhage during the 3-month treatment period in 138 patients with cancer and VTE treated with warfarin and enoxaparin.**

**FIGURE 3. Kaplan–Meier estimates of the probability of symptomatic recurrent VTE among patients with cancer, according to whether they received secondary prophylaxis with dalteparin or OAC therapy for acute VTE.**

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DALTEPARIN AND COUMARIN GROUPS (39% AND 41%). THE AUTHORS CONCLUDED THAT THE LMWH WAS MORE EFFECTIVE THAN COUMARIN AT REDUCING RISK OF RECURRENT VTE WITH NO INCREASED RISK OF BLEEDING.

Hull et al conducted a multicenter, randomized, open-label trial comparing long-term tinzaparin with usual-care (heparin/warfarin) treatment in patients with cancer (Table 2). In the study, 200 patients with cancer and acute symptomatic proximal-vein thrombosis were randomly assigned to receive tinzaparin or usual care for 3 months. At 1-year follow-up, 16% of the usual-care group had recurrent VTE compared with 7% of the LMWH group (P = 0.044; relative risk, 0.56). Bleeding events, mostly minor, were similar in both groups, and major bleeding was infrequent. LMWH was deemed by the authors as more effective than usual care for preventing recurrent VTE in patients with cancer.

ACCP, ASCO, and NCCN guidelines for treatment of VTE in patients with cancer reflect the knowledge gained from the Meyer, Lee, and Hull studies. ACCP guidelines recommend LMWH for the first 3 to 6 months of long-term anticoagulant therapy in patients with cancer and DVT, with subsequent anticoagulant therapy with vitamin K antagonists or LMWH until the cancer is resolved. ASCO guidelines state that LMWH is the preferred approach for the first to 10 days of anticoagulant treatment in patients with cancer and VTE, with LMWH given for at least 6 months for long-term therapy. ASCO guidelines also indicate that vitamin K antagonists can be used for long-term therapy “when LMWH is not available.” NCCN guidelines similarly recommend LMWH for at least 3 months for treatment of VTE in patients with cancer and recommend continuing indefinite anticoagulation for patients with active cancer or other persistent risk factors.

The use of inferior vena cava (IVC) filters, both retrievable and permanent, cannot substitute for antithrombotic therapy in patients with cancer unless there is an appropriate indication. In a study of 166 patients with cancer in whom VTE occurred, 17% of those who had an IVC filter developed thromboembolic complications. Anticoagulation is more effective than an IVC filter in patients with central nervous system tumors, and the risk of post-placement complications was even higher than in other types of cancer. IVC filters should be used only if there is an absolute contraindication to anticoagulation or failure of anticoagulation, and anticoagulation should be resumed as soon as the clinical situation allows. Retrieval filters are a relatively new option. If the need for long-term filter placement is not anticipated, a retrievable filter may be more appropriate in that it can be safely removed when the patient is stable on anticoagulation.

ACCP guidelines also recommend the use of graduated elastic support stockings in patients who have had symptomatic proximal DVT. Compression therapy should be initiated as soon as feasible after the start of anticoagulant therapy and continued for at least 2 years. (“Feasible” refers to the ability of the patient/caregiver to apply and remove the stockings.)

The Use of Antithrombotic Therapy in Patients with Brain Tumors

Patients with brain tumors (primary and metastatic lesions) experience very high rates of VTE—20% to 29% in glioma and 18% to 60% in patients with primary central nervous system lymphoma. Hemorrhage is rare with anticoagulation therapy, however, intracranial hemorrhage occurred in 1.9% of patients with glioma who received anticoagulation versus spontaneous glioma bleeding in 2.2% of patients who did not receive anticoagulation. For most patients, the risk of recurrent VTE outweighs the risk of bleeding. Anticoagulation should be avoided only in tumors associated with a high risk of bleeding, such as melanoma, renal cancer, choriocarcinoma, and thyroid cancer. Physicians should obtain a head computed tomography scan to rule out bleeding. Although LMWH is used as initial therapy in other patients with cancer and VTE, its longer half-life, less complete protamine reversibility, and more cumbersome methods of laboratory monitoring make it a second-line choice in this group. If anticoagulation is to be initiated in patients with brain tumors, physicians should consider starting with UFH for the first 24 hours, and whether it is well tolerated, switching to long-term treatment with LMWH. Using a full bolus of UFH produces an excessive degree of anticoagulation early on, and some experts suggest using a mini bolus (~40 units/kg) unless there is a very high-risk thrombotic state. An IVC filter is indicated if anticoagulation is deemed to be too risky. Some studies even suggest equivalent long-term outcomes in brain cancer patients with DVT treated with an IVC filter versus anticoagulation.

SUMMARY

Patients with cancer have an increased risk of developing VTE, yet prophylaxis is underused. Contributing factors include underrecognition of the additional, unwarranted concern over potential risks of bleeding as compared with the demonstrated benefit of prophylaxis, and lack of awareness of thromboprophylaxis guidelines. The ASCO, NCCN, and ACCP guidelines provide extensive information for the prophylaxis and treatment of VTE in this population.

REFERENCES


