

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer

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H&O What are the concerns regarding thromboembolic events unique to patients with cancer?

AK The first issue for patients with cancer regarding symptomatic venous thromboembolism (VTE) is that it is a quite common problem—though it is unknown how common—based on historic literature. The incidence of VTE appears to be dependent on the disease stage, histology, and the type of cancer treatment received (ie, surgical intervention or different types of chemotherapies or biologic therapies). The risk of VTE therefore varies based on different settings, including perioperatively, during a stay in the hospital, in the outpatient clinic, or in the setting of acute illness associated with a patient's malignancy. Secondly, if a cancer patient develops a thrombosis, compared to a noncancer patient, he or she is three times as likely to experience recurrent thrombosis, despite receiving anticoagulant therapy, and is twice as likely to experience clinically important bleeding associated with anticoagulant therapy. Overall, VTE in patients with cancer represents an important challenge for treating clinicians. This problem is common and difficult to treat. Moreover, published data suggest that cancer patients who develop a blood clot have worse outcomes in terms of long-term survival than those who do not develop a clot.

H&O Why are cancer patients more likely to develop VTE?

AK It is understood that cancer patients are hypercoagulable. This state, which therefore leads to an increased risk of thrombosis, appears to be associated to some extent with tumor elaboration and procoagulant factors, such as tissue factor, which activate coagulation. Tissue factor is also activated as part of the host response to the tumor, which results in the activation of host cells, such as monocytes. In turn, tissue factor is expressed, leading to coagulation.

Beyond this hypercoagulability, cancer patients often have anatomical factors that are associated with heightened risk of thrombosis. For example, a large tumor compressing the pelvic vein or the cava will cause stasis, which increases the risk of intravascular thrombosis. Additionally, cancer patients can be debilitated, which can lead to prolonged immobilization, itself associated with increased risk of thrombosis.

H&O What medical interventions are used to treat patients at risk of thrombosis?

AK Anticoagulants and antithrombotic agents address the hypercoagulability, which reduces the risk of thrombosis. A range of agents has been evaluated, from vitamin K antagonists (eg, warfarin) to low-molecular weight heparins (LMWHs). Researchers have observed particularly successful results in the prevention of thromboembolic events with LMWHs in patients with cancer who have undergone surgery. A LMWH is typically given once daily at a fixed dose after surgery, with the potential for therapy to be extended after the patient has been discharged. The extended use of LMWH is intended to protect against deep vein thrombosis during the recovery period. LMWHs have not been evaluated in medical oncology patients; the only agents tested as

prophylaxis have been the vitamin K antagonists. In a single study, vitamin K antagonists administered to patients with advanced breast cancer showed efficacy in reducing the frequency of VTE. In acutely ill medical patients with cancer admitted to the hospital, LMWHs or unfractionated heparins are recommended as prophylaxis. This recommendation is based on extrapolation from the noncancer population. For the initial treatment of VTE, the usual method is intravenous unfractionated heparin or LMWH. The latter is often preferable because it allows the cancer patient to be dosed without the need for monitoring of the anticoagulant therapy. For long-term prevention of recurrent VTE, vitamin K antagonists or LMWHs can be used. Vitamin K antagonists require monitoring of the international normalized ratio to ensure that it remains in a safe therapeutic range. In contrast, LMWHs are given on a body weight–adjusted basis for up to 6 months. In a study of the LMWH dalteparin (Fragmin, Eisai) given to cancer patients, this agent showed a significant advantage: a 50% reduction in the frequency of recurrent VTE in cancer patients who had suffered a previous thrombosis.

H&O Is heparin-induced thrombocytopenia a concern in cancer patients receiving LMWH?

AK Thrombocytopenia is seen more often with unfractionated heparin than with LMWH. In my view, generally, the thrombocytopenia seen in cancer patients is more likely to be associated with the cancer itself, or with the drugs given to treat the cancer, than with exposure to LMWH. Still, the treating clinician must be sensitive to the risk of heparin-induced thrombocytopenia when using these agents.

H&O Does long-term use of anticoagulants pose any particular risks?

AK With chronic use of heparin, there is a theoretical concern of heparin-associated osteoporosis. Again, this condition is seen more often with unfractionated heparin than with LMWH. With vitamin K antagonists, and any other anticoagulants, the concern about bleeding is always present. In general, in terms of bleeding risk, the LMWHs, however, have a safe profile, even in a high-risk population like the cancer population.

H&O What newer agents are available to prevent and treat thromboembolic events in patients with cancer?

AK New agents, such as inhibitors of factor Xa, have not been specifically evaluated in patients with cancer. At pres-

ent, the efficacy and safety profiles of these agents in this population is unknown. New, oral agents will be evaluated in this population in the near future, and they may offer significant advantages for chronic therapy by virtue of their oral administration. Additionally, LMWHs, due to their pleiotropic nature, may have certain other effects in cancer that may confer additional advantages.

H&O What are the main avenues of research for preventing thromboembolic events in cancer patients?

AK There is some interesting research ongoing in large registries to understand, in a prospective fashion, the frequency of thromboembolic complications seen in cancer patients. Researchers are assessing the effects of variables like the different stages of disease, different types of cancer, and the different interventions used to treat the cancers. These data are needed to understand the true effect of thrombosis on the natural history of disease. Secondly, in terms of innovation, some fascinating, well-designed prospective studies are now ongoing, evaluating the potential benefits of LMWHs to prolong survival in patients with cancer. The early data are not conclusive but they are compelling. These trials are evaluating patients with various tumor types at advanced stages of disease and assigning them to receive LMWH or no antithrombotic intervention on a randomized basis while receiving standard chemotherapy. In this way, the researchers will be able to understand whether the addition of LMWH prolongs survival.

The primary focus of research on the risk of thromboembolic events in cancer has been on solid-tumor malignancies, but there is some evidence that hematologic malignancies, and the treatments used for them, are associated with potential risk of thrombosis. Patients with these malignancies, however, have not yet been the focus of substantial investigation.

Suggested Readings

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