ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

Are Direct Acting Oral Anticoagulants Ready for Prime-Time Use in Cancer-Related Thrombosis?

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H&O How common is thrombosis in patients being treated for cancer?

MS Approximately 20% to 25% of patients with venous thromboembolism (VTE) at a typical anticoagulation clinic will also have a diagnosis of cancer. Large observational studies by Heit and colleagues in the United States and by Blom and colleagues in Europe have shown that as a group, patients with cancer have a 4- to 7-fold increased risk for VTE compared with the general population.

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Different types of cancer vary dramatically in their propensity to cause thrombosis, however. For example, patients with pancreatic cancer have a 15- or 16-fold increased risk, those with brain tumors have a 10-fold increased risk, and those with lung cancer have a 7-fold increased risk. Patients with breast cancer or prostate cancer have a lower increased risk for thrombosis, along the lines of 2- to 3-fold.

Another factor that plays a role in thrombosis risk is disease stage. Patients with metastatic cancer are at much higher risk for thrombosis than are patients with localized disease. A population-based study by Cronin-Fenton and colleagues from Denmark, which maintains an extensive patient database, found that patients with stage IV cancer have a 17-fold increase in thrombosis risk, whereas those with localized cancer have a 2- to 3-fold increase in risk.

H&O What factors make thrombosis more likely to develop in patients with cancer?

MS Unfortunately, many of the treatments we provide to patients with cancer increase the risk for VTE. Having surgery approximately doubles the risk for deep vein thrombosis (DVT) or pulmonary embolism (PE), as does chemotherapy. Another treatment that increases the risk for VTE is hormonal therapy, such as tamoxifen. With all these treatments, most of the increase in risk occurs up front—usually within the first 3 months—and diminishes over time, as shown by Walker and colleagues in a study published in *Blood* in 2016. Other medications used to support patients with cancer, such as the erythropoiesis-stimulatory agent erythropoietin, also increase the risk for VTE.

Factors unrelated to patients' cancer may also increase their risk for thrombosis, such as factor V Leiden. An underlying mutation such as this exerts a synergistic effect together with temporal risk factors to increase the risk for thrombosis during cancer treatment.

Central venous catheters, which are commonly used to administer chemotherapy, increase the risk for blood clots. Finally, the immunomodulatory agents—thalidomide, lenalidomide (Revlimid, Celgene), and pomalidomide (Pomalyst, Celgene)—increase the risk for VTE when used in combination with high doses of dexamethasone or in combination with chemotherapy.

H&O What is the standard treatment for VTE associated with cancer?

MS Until now, the standard first-line treatment has been low-molecular-weight heparin (LMWH)—either dalteparin (Fragmin, Pfizer), enoxaparin (Lovenox, Sanofi-Aventis), or tinzaparin (Innohep, Leo Pharma). The best data we have come from the CLOT trial (Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer), which studied dalteparin, and the CATCH study (Tinzaparin vs Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer), which studied tinzaparin (Table). Many people extrapolate the results obtained with dalteparin to enoxaparin, which is the most widely used of the LMWHs in the United States.

Warfarin and the direct oral anticoagulants (DOACs) have been considered second-line agents. The DOAC dabigatran (Pradaxa, Boehringer Ingelheim) is a direct thrombin inhibitor, whereas the DOACs rivaroxaban (Xarelto, Janssen), apixaban (Eliquis, Bristol-Myers Squibb/Pfizer), and edoxaban (Savaysa, Daiichi Sankyo) are all direct factor Xa inhibitors.

DOACs are appealing because they are not affected by diet and have far fewer drug-drug interactions than do warfarin and other vitamin K antagonists. However, many physicians have been reluctant to use DOACs to treat most patients with cancer and VTE until comparative studies with LMWH are completed.

H&O What are the disadvantages of treatment with LMWH?

MS First, it is expensive—not all insurance plans cover the costs of therapy. Second, it requires several months of injections that can lead to bruising, particularly in the presence of a low platelet count. In fact, studies have shown that many patients who begin treatment with an LMWH for their blood clot eventually switch over to oral agents during the initial 6-month course of treatment. Some studies have shown that nearly half of patients switch.

H&O What makes DOACs different from older agents?

MS Unlike warfarin, which interferes with the production of clotting factors, DOACs are direct inhibitors of clotting factor activity. Consequently, DOACs work much faster than warfarin. It takes 1 to 2 weeks for warfarin to begin working, so patients must use a short-acting anticoagulant such as intravenous heparin or an LMWH until their warfarin level is high enough for protection. The DOACs begin working as soon as they are absorbed, so anticoagulation is complete within hours after the pill has been taken. You can send patients home from the clinic with a prescription, and they can start treating their thrombosis at home—no waiting or measuring blood levels. Also, there are far fewer drug interactions with DOACs than with warfarin, and no dietary restrictions are required.

H&O Are there any differences in safety and efficacy between the 2 types of DOACs—factor Xa inhibitors and thrombin inhibitors?

MS Dabigatran has been associated with more gastrointestinal bleeding than the other DOACs, but all of them are less likely than warfarin to cause intracranial hemorrhages and fatal hemorrhages.

H&O What is the best way to prevent blood clots in high-risk patients who are being treated for cancer?

MS Patients who have myeloma and are receiving cancer regimens associated with a high risk for thrombosis often receive VTE prophylaxis with an LMWH. Another approach is to consider alternative, equally effective treatment regimens that are associated with a lower risk for thrombosis. For example, myeloma regimens that contain bortezomib (Velcade, Millennium/Takeda Oncology) appear to be associated with a lower risk for thrombosis than are comparable immunomodulatory imide (IMiD) drug regimens without bortezomib. In addition, reducing the dose of dexamethasone in a treatment regimen can reduce the risk.

H&O What special concerns exist when VTE is treated in patients with cancer?

MS Chemotherapy-induced thrombocytopenia is an important concern during the treatment of patients with cancer and VTE. Severe thrombocytopenia (platelet count <50,000/μL) significantly increases the risk for bleeding. Management strategies in this situation include platelet transfusions and reduced-dose anticoagulation until platelet count recovery. It remains unclear which management approach is best. This is an area of active investigation.

Table. Results of Major Trials Comparing Low-Molecular-Weight Heparin vs Oral Anticoagulants for the Treatment of Cancer-Associated Venous Thromboembolism

	CLOT, 2003	CATCH, 2015	Hokusai VTE Cancer, 2017	Select-D, 2017
Patients, No.	676	900	1050	406
Age, y (SD)	Dalteparin: 62 (12) VKA: 63 (13)	Tinzaparin: 59.7 (12.7) Warfarin: 58.8 (12.5)	Edoxaban: 64.3 (11.0) Dalteparin: 63.7 (11.7)	67 (range, 22-87)
Metastatic disease, No. (%)	455 (67.3%)	492 (54.7%)	554 (53%)	240 (59%)
Recurrent VTE, No. (%)	Dalteparin: 27 (8%) VKA: 53 (15.8%) HR, 0.48 (95% CI, 0.30-0.77)	Tinzaparin: 31 (6.9%) Warfarin: 45 (10%) HR, 0.65 (95% CI, 0.41-1.03)	Edoxaban: 41 (7.9%) Dalteparin: 59 (11.3%) HR, 0.71 (95% CI, 0.48-1.06)	Dalteparin: 11% (95% CI, 7%-17%) Rivaroxaban: 4% (95% CI, 2%-9%)
Major bleeding, No. (%)	Dalteparin: 19 (5.6%) VKA: 12 (3.6%) *P*=.27	Tinzaparin: 12 (2.7%) Warfarin: 11 (2.4%) *P*=.77	Edoxaban: 36 (6.9%) Dalteparin: 21 (4.0%) HR, 1.37 (95% CI, 1.03-3.04)	Dalteparin: 6 (3%) (95% CI, 1%-6%) Rivaroxaban: 8 (4%) (95% CI, 2%-8%)
Clinically relevant non-major bleeding, No. (%)	NR	Tinzaparin: 49 (10.9%) Warfarin: 69 (15.3%) HR, 0.58 (95% CI, 0.40-0.84); *P*=.004	Edoxaban: 76 (14.6%) Dalteparin: 58 (11.1%) HR, 1.38 (95% CI, 0.98-1.94)	Dalteparin: 5 (2%) (95% CI, 1%-6%) Rivaroxaban: 27 (13%) (95% CI, 9%-19%)
Mortality at 6 mo, No. (%)	Dalteparin: 130 (39%) VKA: 136 (41%) *P*=.53	Tinzaparin: 150 (33.4%) Warfarin: 138 (24.4%) HR, 1.08 (95% CI, 0.85-1.36); *P*=.54	Edoxaban: 206 (39.5%) Dalteparin: 192 (36.6%) HR, 1.12 (95% CI, 0.92-1.37)	Dalteparin: 30% Rivaroxaban: 26%

HR, hazard ratio; mo, months; NR, not reported; SD, standard deviation; VKA, vitamin K antagonist; VTE, venous thromboembolism; y, years.

Sources: Lee AY et al. *N Engl J Med*. 2003;349(2):146-153; Lee AYY et al. *JAMA*. 2015;314(7):677-686; Raskob GE et al [published online December 12, 2017]. *N Engl J Med*; Young A et al [ASH abstract 625]. *Blood*. 2017;130(1)(suppl).

Another important concern is the risk for drug-drug interactions, which are a common problem for patients on warfarin. For example, dexamethasone can interact with warfarin, causing the international normalized ratio (INR) to go up. The drugs 5-fluorouracil and gemcitabine and some antiemetics also can cause an increase in the INR in patients on warfarin. Fewer drug-drug interactions occur with the DOACs, but we know considerably less about the significance of drug interactions with the DOACs than we do about those with warfarin and other vitamin K antagonists.

With oral medications in patients who have cancer, we also need to be concerned about nausea and vomiting. Although the antiemetic regimens have improved immensely, patients who rely on oral anticoagulants are at risk for recurrent events if they are unable to hold down a pill. Absorption of an oral agent also may be problematic in patients who have undergone resection of a large portion of the upper intestinal tract because this is where the DOACs and warfarin are absorbed. More data on this issue are needed to guide clinicians.

Another concern is organ dysfunction. LMWH, and to a varying extent the DOACs, are excreted by the kidneys. Therefore, close attention to renal function is important when LMWH or a DOAC is being considered for the treatment of VTE in patients with cancer. Liver function is also important for the clearance of warfarin as well as the DOACs. Recent randomized controlled trials with DOACs excluded patients with poor renal function (Cockcroft-Gault estimated creatinine clearance <25-30 mL/min) and poor hepatic function (liver transaminase level >2-3 times the upper limit of normal or total bilirubin level >1.5 times the upper limit of normal). As a result, it is important to make sure your patient fits the

inclusion/exclusion criteria used to study the medication being considered for VTE treatment. Otherwise, results may not be comparable. I would be hesitant to use liver-metabolized anticoagulants in patients whose tumors involve a significant portion of the liver.

H&O How safe and effective are DOACs in treating thrombosis in patients with cancer?

MS Until recently, the only information we had on the efficacy and safety of the DOACs in the treatment of VTE in patients with cancer came primarily from the large randomized trials conducted to gain approval of the Food and Drug Administration. In general, these studies included a small number of patients with active cancer, although the definition of active cancer varied from study to study and was different from the definition used for the CLOT and CATCH studies. In these small groups of patients, DOACs appeared to be as efficacious as warfarin—with a trend toward greater efficacy in regard to bleeding and recurrent thrombosis. The fact that the trends were not statistically significant likely reflects the fact that the number of patients who had cancer was small.

These data were supplemented by several single-institution cohort studies. Mantha and colleagues at Memorial Sloan Kettering Cancer Center reported in early 2017 in the *Journal of Thrombosis and Thrombolysis* on a cohort of 200 consecutive patients who had cancer and VTE treated with rivaroxaban. They found that the cumulative incidence of new or recurrent cases of VTE at 6 months was 4.4%, and the rate of major bleeding was 2.2%. Similar results were noted by Bott-Kitslaar and colleagues at the Mayo Clinic. Although these data are very reassuring, they are based on single-arm studies without an LMWH comparator group. Therefore, I think that many physicians are awaiting data from the randomized controlled trials comparing a DOAC with LMWH in patients with active cancer and acute VTE.

These data were provided by 2 studies presented at the 2017 annual meeting of the American Society of Hematology (ASH). In the late-breaking abstract session, Gary Raskob, PhD, presented the results of the Hokusai VTE Cancer trial (Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism), which was simultaneously published in the *New England Journal of Medicine*. In an open-label noninferiority trial, the investigators randomly assigned 1050 patients with active cancer and acute VTE either to the LMWH dalteparin (200 U/kg subcutaneously once daily for 1 month followed by 150 U/kg subcutaneously once daily) or to the LMWH dalteparin for 5 days, followed by 60 mg of edoxaban by mouth daily (30 mg daily in patients with a creatinine clearance of 30-50 mL/min or weight <60 kg or undergoing concomitant treatment with a potent p-glycoprotein inhibitor) for up to 12 months. The primary outcome was the composite endpoint of recurrent symptomatic VTE or major bleeding. The primary outcome occurred in 67 patients treated with edoxaban (12.8%) and 71 patients treated with dalteparin (13.5%), establishing noninferiority (hazard ratio [HR], 0.97; 95% CI, 0.70-1.36; P=.0006 for noninferiority). VTE recurred in 41 patients given edoxaban (7.9%) and in 59 patients given dalteparin (11.3%), for an absolute difference in risk of 3.4% (95% CI, 0.2%-7.0%). Major bleeding occurred in 36 edoxaban patients (6.9%) and 21 dalteparin patients (4.0%), for an absolute difference in risk of 2.9% (95% CI, 0.1%-5.6%) Clinically relevant nonmajor bleeding occurred in 76 edoxaban patients (14.6%) and in 58 dalteparin patients (11.1%) (HR, 1.38; 95% CI, 0.98-1.94). Patients who had gastrointestinal cancer were more likely to experience bleeding with edoxaban than with dalteparin. This study demonstrates that oral edoxaban is noninferior to LMWH dalteparin for the treatment of cancer-associated venous thromboembolism.

At ASH, in Monday morning's oral session on antithrombotic therapy in cancer, Annie Young, PhD, presented the results of the Select-D pilot trial (Anticoagulation Therapy in Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism). In this prospective open-label study, investigators randomly assigned 406 patients with cancer-associated VTE either to rivaroxaban (15 mg by mouth twice daily for 21 days, followed by 20 mg daily) or to the LMWH dalteparin (200 U/kg subcutaneously once daily for 1 month, followed by 150 U/kg subcutaneously daily in months 2-6). At 6 months, VTE had recurred in 4% of patients taking rivaroxaban (95% CI, 2%-9%) and in 11% of patients taking dalteparin (95% CI, 7%-17%). Major bleeding occurred in 8 patients taking rivaroxaban (4%; 95% CI, 2%-8%) and in 6 patients taking dalteparin (3%; 95% CI, 1%-6%). Clinically relevant nonmajor bleeding occurred in 27 patients taking rivaroxaban (13%; 95% CI, 9%-19%) and in 5 patients taking dalteparin (2%; 95% CI, 1%-6%). Gastrointestinal sites were a common location of bleeding. The results of this randomized pilot study support the data from previously published single-center studies suggesting that rivaroxaban is an attractive oral option for the treatment of cancer-associated VTE.

H&O Would you say that DOACs are ready for prime-time use in patients with cancer?

MS In light of the data from the Hokusai VTE Cancer trial and supportive data from the Select-D pilot study, I

think we have to consider edoxaban and rivaroxaban as viable alternatives to LMWH in the treatment of cancer-associated VTE. This change will have significant benefits for our patients because we will be able to switch from treatment with LMWH, which is expensive and requires daily injections, to an oral therapy. To optimize patient outcomes, I think it will be important to adhere closely to the inclusion and exclusion criteria used in these studies. In addition, I would be cautious when using DOACs in patients with gastrointestinal cancers because bleeding increased in these patients when they were treated with DOACs. Further results from subgroup analyses of these studies and other ongoing studies will undoubtedly refine our approach to the treatment of cancer-associated VTE and maximize the number of patients eligible for DOAC therapy.

H&O What should the next step in research be?

MS I think we need to continue to investigate the role of DOACs in cancer-associated VTE to refine our approach. Several studies of DOACs for cancer-associated VTE are ongoing. CASTA-DIVA (Cancer Associated Thrombosis, a Pilot Treatment Study Using Rivaroxaban; NCT02746185) and CONKO-011 (Rivaroxaban in the Treatment of Venous Thromboembolism in Cancer Patients; NCT02583191) are comparing rivaroxaban vs LMWH, and Caravaggio (Apixaban for the Treatment of Venous Thromboembolism in Patients With Cancer; NCT03045406) is comparing apixaban vs the LMWH dalteparin. These studies will help us to understand which patients will do best with DOAC therapy and which patients will be better treated with LMWH. We also need to continue doing real-world observational studies, such as GARFIELD-VTE (Global Anticoagulant Registry in the FIELD- Venous Thromboembolic Events; NCT02155491) and XALIA (Treatment of an Acute Deep Vein Thrombosis With Either Rivaroxaban or Current Standard of Care Therapy; NCT01619007), to better understand how DOACs work in the broader population of patients with cancer. This is important because some of them are not eligible for inclusion in randomized controlled trials.

Currently, there are no data regarding the utility of DOACs in the prevention of central venous catheter–associated thrombosis. This is another area of cancer-associated thrombosis that warrants further investigation. Acquiring more data will help us to improve the treatment of cancer-associated VTE.

Suggested Readings

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