Treating Venous Thrombosis in Oncology

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With the oncology landscape changing rapidly, effective care requires bringing clarity to complex data, and this is especially true for the treatment of venous thromboembolism (VTE) in cancer. Although newer options may make therapy easier to use, said Rowena Schwartz, PharmD, BCOP, of the University of Cincinnati, providers must make sure not to oversimplify the information such that they overlook potential risks and complications in this population. At JADPRO Live 2018, Dr. Schwartz shared recent findings comparing the safety and efficacy of "standard" anticoagulants with those of direct oral anticoagulants (DOACs), discussed the risks and benefits of treatment of DOACs, and detailed how to monitor and assess patient response to anticoagulant treatment.

"When we talk about data, we're often talking about the results of clinical trials that include a population, but when you and I go into practice, it is the individual that we're actually looking at," said Dr. Schwartz. "I get worried if we just look at the data from studies when it doesn't fit the unique aspects of the patients we treat."

RISK FACTORS FOR VTE IN PATIENTS WITH CANCER

As Dr. Schwartz explained, many of the risk factors for VTE in the patient with cancer are related to specific cancer types; head and neck cancer has the lowest risk, for example, while pancreatic cancers and central nervous system malignancies carry increased risk. However, one of the key factors is active disease (Rocha et al., 2007). There are also treatment-related risks. A number of different agents carry VTE risk, such as immunomodulatory drugs (e.g., thalidomide, lenalidomide [Revlimid], pomalidomide [Pomalyst]) and dexamethasone, hormones (e.g., estrogens, progestins), selective estrogen receptor modulators (e.g., tamoxifen), vascular endothelial growth factor (VEGF) inhibitors (e.g., bevacizumab [Avastin]), and erythropoietin-stimulating agents.

PHARMACOTHERAPY OPTIONS FOR VTE

According to Dr. Schwartz, it is important to consider broad treatment options because the new treatments that are used in VTE, the DOACs, are not the answer for everyone.

"As more and more providers embrace direct oral anticoagulants,

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which don't require aggressive monitoring, I am concerned that people are losing the ability to monitor the older agents appropriately and effectively," said Dr. Schwartz.

Heparin

As Dr. Schwartz explained, unfractionated heparin, a large molecule and a biologic, was the gold standard for VTE treatment. One of the adverse events unfractionated heparin causes is hypersensitivity reaction, and there can be antibodies associated with it, as well. Although bleeding is a risk associated with unfractionated heparin, said Dr. Schwartz, this risk deceases with the discontinuation of therapy. Low-molecular-weight heparin, on the other hand, is smaller (about one third of the size) and is less commonly associated with thrombocytopenia.

"When we go to low-molecular-weight heparin, our focus tends to be much more on factor Xa and thrombin," said Dr. Schwartz, who noted that one of the key benefits of heparin is a short half-life, which is important for bridging patients and for certain other types of procedures.

Protamine sulfate is an effective reversal agent used with heparin but should be avoided in patients who have shellfish allergies, have had vasectomies, or have been on insulin.

Given the mechanism of action, low-molecular-weight heparin also increases the interaction of antithrombin and factor Xa. Dr. Schwartz also noted that clearance is not dependent on dose, so low-molecular-weight heparin needs to be monitored in most patients in a similar way to patients on unfractionated heparin. Nevertheless, said Dr. Schwartz, the drug is relatively predictable, which is one of the reasons it is so frequently used as initial therapy for VTE as well as longer-term treatment of VTE in patients with cancer.

"With respect to VTE treatment doses, factors such as obesity and renal impairement may be important," Dr. Schwartz noted. "It's also important to realize that the doses on the package insert are not the long-term dose used in most patients with cancer-associated VTE."

Finally, heparin carries an increased risk of osteoporosis with prolonged use. When low-molecular-weight heparin is used for 6 to 12 months or beyond, the risk of osteoporosis is something that we should be considering, said Dr. Schwartz.

Targeting Factor Xa

There are currently four factor Xa inhibitors on the market used for the treatment of VTE, including one agent administered subcutaneously (fondaparinux) and three oral drugs (rivaroxaban, apixaban, and edoxaban). With respect to the oral agents, Dr. Schwartz emphasized the difference in dosing. One of the key things with edoxaban, she said, is the use of a lead-in of a low-molecular-weight heparin or unfractionated heparin before initiation of the oral drug (60 mg daily). With rivaroxaban, there is a lead-in period of 21 days (15 mg twice daily) followed by 20 mg once per day. With apixaban, there is a lead-in period of 7 days (10 mg twice daily) followed by 5 mg twice daily.

"This dosing can lead to a lot of confusion," Dr. Schwartz explained. "These are not drugs like antibiotics that patients are familiar with, so they really do require the same education used for warfarin or low-molecular-weight heparin."

The Gold Standard for VTE Treatment

While vitamin K antagonist (warfarin) used to be the gold standard for VTE treatment, this shifted with the publication of the results of the CLOT Trial in 2003, which demonstrated significant benefits in the risk of recurrent VTE and major bleeding events with low-molecular-weight heparin (Lee et al., 2003). However, as Dr. Schwartz reported, data comparing low-molecular-weight heparin and DOACs are wanting.

A pilot study (SELECT-D Trial) recently conducted in the United Kingdom looked at rivaroxaban vs. low-molecular-weight heparin in approximately 460 patients (Young et al., 2018). The treatment duration was 6 months and the primary outcome was VTE recurrence. Authors of the study concluded that DOACs had lower recurrent VTE at 6 months compared to low-molecular-weight heparin but higher major bleeding and clinically relevant nonmajor bleeding events.

"The bleeding that mainly occurred was GI [gastrointestinal] bleeding in patients with GI tumors," said Dr. Schwartz, who added that there is now a warning in the Guidelines to be cautious of patients at risk for GI bleeding.

According to Dr. Schwartz, one of the biggest questions in cancer is "How long should patients remain on treatment?" A study of edoxaban vs.

low-molecular-weight heparin found that patients stayed longer on the oral agent than they did on the injection (Raskob et al., 2018), "which is hardly shocking," Dr. Schwartz observed.

"If you look at the NCCN Guidelines, one of the key things is to identify patients who are on chronic anticoagulation, as people tend to forget what they're taking medications for," said Dr. Schwartz. "It's pretty easy for people to remember they're on an anticoagulant if they're giving themselves shots but not necessarily so if they're taking oral drugs."

ANTICOAGULATION AT EXTREMES OF BODY WEIGHT

Another question that often comes up is "Which populations does this not work for?" Dr. Schwartz emphasized that it is important to consider patients at extremes of body weight when administering these medications.

"The numbers vary," said Dr. Schwartz. "Some people use under 50 kilos and over 120 kilos as cutoffs, but it's important to consider patients who are either very small or very big because these doses are flat dosed and determined for the general population."

Ultimately, said Dr. Schwartz, when thinking about the management of VTE in your patient with cancer, the key thing is to study the evidence when selecting agents, understand the risk of bleeding, and then examine individual patient factors.

Disclosure

Dr. Schwartz has no conflicts of interest to disclose.

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