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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Can I use direct oral anticoagulants to treat cancer-associated venous thromboembolism?

A: Yes. The direct oral anticoagulants rivaroxaban, edoxaban, and apixaban have been studied in cancer-associated venous thromboembolism and are increasingly replacing low-molecular-weight heparins such as dalteparin and enoxaparin for this purpose. Individualizing care by balancing risks and benefits for each patient will help in choosing the right anticoagulant.

LOW-MOLECULAR-WEIGHT HEPARINS

The National Comprehensive Cancer Network guidelines previously recommended low-molecular-weight heparins as the preferred anticoagulants for cancer-associated venous thromboembolism, but now they are one of several first-line options.[1]

Before the advent of direct oral anticoagulants, low-molecular-weight heparins were recommended over vitamin K antagonists such as warfarin because they were more effective. This recommendation was supported by a large randomized trial,[2] in which the recurrence rate was significantly lower in patients treated with dalteparin than in those receiving vitamin K antagonists, with no significant difference in major bleeding between the 2 treatment groups. The number needed to treat to prevent 1 recurrence of venous thromboembolism was 13.[2]

An important advantage of low-molecular-weight heparins over vitamin K antagonists is that their anticoagulant effect does not routinely need to be monitored, whereas vitamin K antagonists require monitoring of the international normalized ratio. Low-molecular-weight heparins are, however, contraindicated in patients with severe kidney disease because these drugs are cleared renally.

RIVAROXABAN

Rivaroxaban, a direct-acting factor Xa inhibitor, is given twice daily for the first 3 weeks and then once daily thereafter when used to treat venous thromboembolism.[3] In this situation, it should be taken with food, which improves its absorption.[3]

In a randomized clinical trial,[4] rivaroxaban was more effective than dalteparin at reducing the recurrence of venous thromboembolism in cancer patients but was associated with higher rates of major bleeding and clinically relevant nonmajor bleeding. The number needed to treat to prevent 1 recurrence was 20, while the number needed to harm to cause 1 major bleed was 50.[4]

The risk of bleeding is higher with gastrointestinal and genitourinary tract cancer, and this increased risk should be borne in mind when choosing a direct oral anticoagulant for venous thromboembolism.[1]

EDOXABAN

Edoxaban is an oral direct factor Xa inhibitor that has been studied for the treatment of cancer-associated venous thromboembolism. When initiating edoxaban therapy, a parenteral anticoagulant should be given for at least 5 days before transitioning to edoxaban.[5] It is given as a once-daily dose and offers the convenience of oral route of administration.[5]

Rivaroxaban, edoxaban, and apixaban are increasingly replacing low-molecular-weight heparins

Dr. Emiloju has disclosed consulting for GlaxoSmithKline.

doi:10.3949/ccjm.87a.19100

In the Hokusai trial,[6] edoxaban was found to be noninferior to dalteparin for the composite end point of recurrent cancer-associated venous thromboembolism (hazard ratio 0.97, 95% confidence interval 0.70–1.36, calculated number needed to treat 29). There was, however, a higher rate of major bleeding, especially from the upper gastrointestinal tract, with edoxaban than with dalteparin (calculated number needed to harm 34). Patients with gastrointestinal cancers were more likely to experience major gastrointestinal bleeding in the study. Thus, edoxaban should be used with caution in this patient group.

APIXABAN

Apixaban, another oral direct factor Xa inhibitor, is taken twice a day when used to treat venous thromboembolism.[7] It also offers the advantage of an oral route of administration. But its twice-a-day dosing makes it less convenient than rivaroxaban or edoxaban.

A pilot randomized controlled trial compared apixaban with dalteparin in the treatment of cancer-associated venous thromboembolism and found that rates of recurrence and major bleeding were lower with apixaban.[8]

Gastrointestinal lesions are relative contraindications to the use of direct oral anticoagulants

A larger trial called CARAVAGGIO (NCT03045406) comparing apixaban with dalteparin in cancer-associated venous thromboembolism is under way, and trial results are awaited.

The National Comprehensive Cancer Network guidelines already recommend apixaban for cancer-associated venous thromboembolism,[1] but other societies such as the American Society for Clinical Oncology do not.[9] It will be important to assess the safety of apixaban in patients with gastrointestinal and genitourinary cancers in light of what we already know from trials of other direct factor Xa inhibitors such as edoxaban and rivaroxaban.

DABIGATRAN

Dabigatran is a direct thrombin (factor IIa) inhibitor that has not been specifically studied in cancer patients. There was, however, a subgroup analysis of cancer patients enrolled in a larger venous thromboembolism trial.[10] Initial parenteral anticoagulation for at least 5 days was followed by either dabigatran or warfarin. In the analysis of the cancer population within the study, there was no significant difference in recurrence and major bleeding rates between the dabigatran and warfarin groups.[10]

Major limitations of this study were that dabigatran was not compared with a low-molecular-weight heparin, which is the standard of care, and the study was not prospectively designed to study cancer-associated venous thromboembolism.

CONTRAINDICATIONS TO DIRECT ORAL ANTICOAGULANTS

Renal impairment

The direct factor Xa inhibitors are partially cleared by the kidneys, so renal function is important.

Edoxaban requires a dose reduction in patients with creatinine clearance 15 to 50 mL/min and is contraindicated in patients with creatinine clearance below 15 mL/min.[5]

Rivaroxaban is contraindicated if creatinine clearance is less than 30 mL/min, and the manufacturer recommends caution if creatinine clearance is 30 to 50 mL/min.[3]

Apixaban's manufacturer does not recommend any dose reduction with renal impairment, but patients with creatinine clearance below 15 mL/min were not included in the randomized controlled trial of this drug.[7]

Liver impairment

Given that coagulopathy is frequently associated with liver disease and that some direct oral anticoagulants are partially cleared in the liver, hepatic impairment is an important contraindication to their use.

Apixaban requires no dose adjustment in mild hepatic impairment (Child-Pugh class A) and is contraindicated in severe hepatic impairment (Child-Pugh class C).[7]

Edoxaban and rivaroxaban are contraindicated in moderate and severe hepatic dysfunction (Child-Pugh classes B and C).[3,5] The guidelines recommend not giving apixaban and edoxaban if aminotransferase levels are more than twice the upper limit of normal, while rivaroxaban is contraindicated if they are more than 3 times the upper limit of normal.[1]

Other contraindications

Gastrointestinal lesions such as cancers, ulcers, and varices and recent instrumentation

are relative contraindications to direct oral anticoagulants in cancer-associated venous thromboembolism because of an increased risk of bleeding.[4,6]

Current guidelines do not recommend direct oral anticoagulants in patients whose body mass index is above 40 kg/m^2 because the initial pharmacokinetic studies of these drugs did not include patients in this category.[9]

Other important considerations in the use of direct oral anticoagulants include potential drug interactions, especially with inducers and inhibitors of the cytochrome P450 3A4 enzymes and the potential nephrotoxicity and hepatotoxicity of concurrent anticancer agents.[1] More frequent monitoring for adverse effects and organ dysfunction is warranted in these instances.

BLEEDING RATES

Compared with low-molecular-weight heparins, rivaroxaban and edoxaban are associated with higher rates of bleeding.[4,6] The risk of bleeding is higher in patients with genitourinary or gastrointestinal abnormalities (eg, cancers, ulcers, varices) and recent instrumentation.[4,6] In these scenarios, the International Society on Thrombosis and Hemostasis recommends low-molecular-weight heparins instead of direct oral anticoagulants, and the choice of anticoagulant should be a shared one between the clinician and the patient.[11]

If life-threatening or uncontrollable bleeding develops in a patient on rivaroxaban or apixaban, andexanet alfa can potentially be used as an antidote, although it has not been studied specifically in patients with cancer-associated venous thromboembolism.[12]

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