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Bleeding Complications With Bruton Tyrosine Kinase Inhibitors

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H&O What types of bleeding complications can occur with Bruton tyrosine kinase (BTK) inhibitors?

TD Bleeding complications are very common and can range from minor "nuisance" bruising to life-threatening bleeds, including intracranial hemorrhage.

H&O How common are bleeding complications with BTK inhibitors?

TD A 2015 study by Wang and colleagues found that after 3 years of follow-up, more than half of patients on ibrutinib (Imbruvica, Pharmacyclics/Janssen) had a bleeding event. The rate is a bit lower now because we are more aware of the risk and have become better at managing it. When it comes to severe hemorrhages, the percentage ranges from approximately 4% to 10%. So bleeding is a potential complication that must be taken into account, especially in older patients and in those who have risk factors for bleeding, such as underlying platelet dysfunction.

H&O What is the mechanism by which BTK inhibitors contribute to bleeding?

TD Multiple mechanisms seem to be at work. BTK inhibitors tend to block multiple pathways that play a part in augmenting platelet function, such as granule release, formation of pseudopods, and binding of collagen. BTK inhibitors also inhibit the TEC tyrosine kinase, which affects platelet activation. These off-target effects are important because patients with congenital BTK deficiency have mild to no bleeding. The effects are more pronounced with ibrutinib than with acalabrutinib (Calquence, AstraZeneca), which has less of an off-target effect, but we still see these issues with acalabrutinib. Another contributing reason for the lower risk for bleeding in trials of acalabrutinib is that we are more aware of the risk now—we avoid entering people in clinical trials of BTK inhibition if they are already at elevated risk for bleeding.

H&O Which patients are most likely to experience bleeding with BTK inhibitors?

TD People with a history of bleeding are at increased risk for bleeding with BTK inhibitors. Older people are at increased risk of bleeding because of their age, and also because they are more likely to be taking medications that affect bleeding, such as anticoagulants, aspirin and certain other nonsteroidal anti-inflammatory drugs, and selective serotonin reuptake inhibitors.

In some cases, patients have unexpected problems with bleeding. Maybe these patients had subtle platelet disorders that never caused a problem until BTK inhibitors were added. But in most cases, the patients who experience bleeding with BTK inhibitors are those in whom we might expect problems, based on their use of other medications. Before physicians prescribe a BTK inhibitor, they need to take a careful history.

H&O Do you recommend any coagulation or platelet function studies before prescribing BTK inhibitors?

TD These studies are less predictive of bleeding than a careful history, so we tend not to use them. The studies can be interesting from a research standpoint, but they are difficult to interpret in day-to-day practice. I am more interested in whether someone has a history of excess bleeding.

H&O Are certain agents contraindicated in patients taking BTK inhibitors?

TD No agents are absolutely contraindicated, but we try to avoid medications such as aspirin and anticoagulants unless they are truly necessary. If a patient who is taking a BTK inhibitor needs to have a cardiac stent implanted, for example, we need to have a conversation with the patient's cardiologist and ensure that the duration of dual antiplatelet therapy is as short as possible. We will often switch to single antiplatelet therapy after just a short time, and we need to reevaluate the need for antithrombotic therapy periodically.

Many of my patients on BTK inhibitors require pain control for arthritis or back problems, so a frequent topic of discussion is the use of nonsteroidal anti-inflammatory drugs. Good choices for these patients are the cyclooxygenase 2 inhibitor celecoxib, which does not interfere with platelet function, and meloxicam, which is an older drug that has very little effect on platelet function. I often use meloxicam because it costs less than celecoxib; interestingly, this is the drug of choice in the military.

We try to plan ahead, but situations arise in which atrial fibrillation develops in someone with a high risk for stroke or deep vein thrombosis, and we have to add anticoagulation on top of BTK inhibition. If that combination causes severe bleeding, we may need to switch from a BTK inhibitor to an alternative drug.

H&O Do you avoid warfarin use entirely?

TD Yes, we rarely use warfarin these days because the direct oral anticoagulants (DOACs) are safer and much easier to use. They are safer when combined with aspirin or other antiplatelet agents, so we believe they would be safer when combined with ibrutinib.

H&O Do you need to worry about agents such as fish oil and vitamin E?

TD We caution patients about overuse of these agents because bleeding with high doses—which would be 3000 U of vitamin E per day and 3 g of fish oil per day—is of some concern. The indications for vitamin E and fish oil are limited, so this provides another opportunity for education.

H&O Should special precautions be taken in patients on anticoagulant or antiplatelet therapy or otherwise at elevated risk for bleeding?

TD The first step I take in this instance is to be sure that the patient absolutely needs the medication. If the patient is taking warfarin, can that be changed to a DOAC? If the person has been taking an antiplatelet agent, is it still needed? The evidence has evolved regarding aspirin for the primary prevention of myocardial infarction; we have found that the risks outweigh the benefits for many patients. Prescribing a BTK inhibitor provides a good opportunity to reassess the other medications that a patient is taking, especially aspirin.

> Patients need to mention their bleeding risk to their other health care providers, especially before surgery, because it has the potential to get overlooked.

H&O When bleeding occurs in patients on BTK inhibitors, how should it be managed?

TD The first step is to halt use of the drug temporarily. If the bleeding is severe, we also administer platelets. The half-life of BTK inhibitors is short, so we do not need to worry about the platelets being inhibited by the BTK inhibitor. Another useful agent for bleeding—including gastrointestinal bleeds and nosebleeds—is tranexamic acid, which we administer either orally (1300 *mg* 3 times daily) or intravenously (1000 *mg*/d). Another possible treatment for bleeding, although it has not been studied specifically with BTK inhibition, is desmopressin.

H&O What are the special concerns related to surgery in patients on BTK inhibitors?

TD We have the same concerns with BTK inhibitors as with any antiplatelet agent. I emphasize to my patients

that BTK inhibitors increase their risk for bleeding, so they need to halt their use of the agent before surgery. Patients must mention their bleeding risk to their other health care providers, especially before surgery, because it is possible for it to be overlooked. I do not want to be called into the operating room because a patient who is on ibrutinib is having life-threatening bleeding during surgery to remove the gallbladder. We usually halt the BTK inhibitor a week before major surgery and resume administration a day or two after surgery, once good hemostasis has been restored.

H&O Could you discuss the relationship between BTK inhibitors and atrial fibrillation?

TD We have been surprised to see that BTK inhibitors increase the risk for atrial fibrillation. The risk is increased by as much as 3-fold with ibrutinib, and less with acalabrutinib, although it is still seen. This is an important issue because atrial fibrillation is a major cause of stroke; 20% of strokes in the United States may be attributed to the condition. Anticoagulation is the treatment of choice for most patients with atrial fibrillation, but we are concerned about adding an anticoagulant to a drug that inhibits platelet function. As a result, the best choice in this situation is to use a DOAC for anticoagulation because the risk for bleeding is lower than with older anticoagulants, such as warfarin.

Another approach to managing atrial fibrillation is to use electric cardioversion to reset the heart rhythm. Patients who undergo this procedure will often need a short-term course of anticoagulation, but at least they will not be taking the drug for the rest of their life. I discuss with the patient's cardiologist the possibility of more aggressive treatment in these cases.

H&O Would you avoid the use of BTK inhibitors in patients with atrial fibrillation who are on aspirin or systemic anticoagulation?

TD I would certainly consider a DOAC for systemic anticoagulation. If a patient absolutely needed to be on aspirin as well, I would say that using a BTK inhibitor would be too much—we would consider that the equivalent of triple-therapy antithrombosis, which carries an unacceptably high risk for bleeding. Studies of triple therapy with aspirin, clopidogrel, and warfarin, or with aspirin, clopidogrel, and a DOAC, show a much-increased rate of bleeding.

H&O Do BTK inhibitors reduce the risk for cardiovascular events?

TD They would in theory, given that they act as antiplatelet agents. I have sometimes made the case to the patient's cardiologist that we can skip the aspirin if the patient is already on apixaban (Eliquis, Bristol Myers Squibb) and ibrutinib. In theory, cardioprotective effects are possible because of the antiplatelet effects, especially via novel pathways, such as inhibiting glycoprotein IV and von Willebrand factor interactions. However, this advantage may be negated by the large number of patients on ibrutinib in whom hypertension develops—as many as 72%, according to a 2019 study by Dickerson and colleagues. In this study, hypertension was associated with an increased risk for cardiac events.

H&O Could you please discuss any drug interactions between BTK inhibitors and cardiac anti-arrhythmics?

TD Ibrutinib is a powerful CYP3A4 inhibitor, so the potential exists for a variety of drug interactions. For example, if a patient on ibrutinib is started on amiodarone, the ibrutinib dose needs to be cut to 280 *mg* daily. The same advice applies when ibrutinib is used with diltiazem, dronedarone (Multaq, Sanofi-Aventis), or verapamil. Given that acalabrutinib is also a CYP3A4 substrate, the same considerations would be in play.

Disclosures

Dr DeLoughery has no relevant disclosures.

Suggested Readings

Dickerson T, Wiczer T, Waller A, et al. Hypertension and incident cardiovascular events following ibrutinib initiation. *Blood*. 2019;134(22):1919-1928.

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