Regorafenib (Stivarga, Bayer) is a once-daily, oral multikinase inhibitor. It first received approval in September 2012 for patients with metastatic colorectal cancer (CRC) who were previously treated with chemotherapy, an anti–vascular endothelial growth factor therapy, and (if KRAS wild-type) an anti–endothelial growth factor receptor therapy. In February 2013, it received approval for patients with locally advanced, unresectable, or metastatic gastrointestinal stromal tumors (GIST) who were previously treated with imatinib and sunitinib (Sutent, Pfizer). More recently, in April 2017, regorafenib was approved for use in patients with hepatocellular carcinoma (HCC) who were previously treated with sorafenib (Nexavar, Bayer).

The most common adverse reactions with regorafenib are pain (including gastrointestinal and abdominal pain), hand-foot skin reaction, asthenia/fatigue, diarrhea, decreased appetite/food intake, hypertension, infection, dysphonia, hyperbilirubinemia, fever, mucositis, weight loss, rash, and nausea. It may also cause hepatotoxicity (called out in a black box warning), infections, hemorrhage, gastrointestinal perforation or fistula, dermatologic toxicity, hypertension, cardiac ischemia and infarction, and reversible posterior leukoencephalopathy syndrome. It also has the potential to cause wound healing complications and embryo-fetal toxicity.

H&O What are the most common adverse events that you see with regorafenib?

TBS The 2 most common adverse events that we see with regorafenib and many other similar tyrosine kinase inhibitors are hand-foot skin reaction and fatigue.

When regorafenib causes hand-foot skin reaction, the condition appears approximately 2 weeks after treatment begins and usually peaks in severity at 3 to 4 weeks. This very bothersome adverse event limits patients’ ability to walk and carry out basic activities of daily living, so it often necessitates pausing treatment or stopping it altogether.

The fatigue from regorafenib can be difficult to pinpoint because patients with advanced CRC or HCC typically have a reduced performance status, and are already quite fatigued.

We see a number of additional toxicities that are relatively manageable and tolerable, such as hypertension and hoarseness. We also see liver toxicity, which in rare cases is severe.

H&O How often do your patients experience hand-foot skin reaction with regorafenib?

TBS Nearly all patients taking regorafenib—probably 80% to 90%—experience some degree of hand-foot skin reaction. The reaction is severe in about 10% to 15%.

H&O How common is fatigue among your patients taking regorafenib?

TBS Approximately 40% of patients taking regorafenib experience a meaningful level of fatigue. In some cases, the fatigue is severe enough that the patient is bedridden.

H&O Are the adverse events that you see in your practice consistent with what is listed in the package insert?

TBS For the most part they are, although of course there is always some variation among practices. Some
practices like to use tyrosine kinase inhibitors in all their eligible patients and others wait until later in the treatment course, when patients have a poor performance status. I tend to use regorafenib in third-line treatment, and I never use it in a patient with a performance status of 2 or higher. Regorafenib tends to have a better toxicity profile and an improved activity level in patients who have a performance status of 0 or 1.

One example of an adverse event listed in the package insert that I have not seen in my own patients is gastrointestinal or abdominal pain.

**H&O** What is your advice for reducing the risk for adverse events from regorafenib?

**TBS** We cannot prevent hand-foot skin reaction in our patients, but we can reduce the risk for a severe reaction by taking several steps.

First, and this is the most important step, we see the patients on a weekly basis during the first 4 weeks of treatment and every 2 weeks during the second 4 weeks of treatment. This allows us to keep a close eye on the patients, check their hands and feet, and draw their blood for laboratory testing. Some physicians and patients think they can get away with just one office visit per month because regorafenib is an oral medication. But if patients develop severe hand-foot skin reaction in those first 4 weeks, they will be in horrendous shape and may wish to stop treatment entirely. Some of them will stop taking the drug on their own. So that first month is critical.

Second, we use a dose-escalation strategy—we start patients with regorafenib at 80 mg/day for the first week, then accelerate the dose to 120 mg/day for the second week and 160 mg/day for the third week, based on tolerability.

In the ReDOS study (Regorafenib Dose Optimization Study), we evaluated a dose-escalation strategy in 123 patients with refractory metastatic CRC. The results, presented at the 2018 Gastrointestinal Cancers Symposium, showed that this strategy improves overall survival and helps patients overcome some of the issues seen when the initial dose is 160 mg/day.

Finally, we educate the patients on what to expect and how to take care of themselves. Patients who are taking regorafenib need to keep their hands and feet moisturized, practice good hygiene, and call us immediately if symptoms begin to appear.

**H&O** How do you manage hand-foot skin reaction in patients taking regorafenib?

**TBS** If patients develop mild hand-foot skin reaction, we focus on the use of moisturizers and occasionally introduce a corticosteroid cream. We continue to educate the patients on how to best take care of their hands and feet, and tell them to let us know if their condition gets worse.

If patients present with a grade 3 or intolerable grade 2 hand-foot reaction, we pause the drug until the condition resolves. Resolution of symptoms usually takes 1 or 2 weeks, after which we restart the medication at a lower dose. Hand-foot reactions usually resolve with this approach but some patients continue to experience reactions even at the lowest dose, so treatment must be stopped.

**H&O** Do you have specific recommendations for dealing with fatigue related to regorafenib?

**TBS** Fatigue is a symptom of underlying disease. Severe fatigue raises concern because it tends to be seen in patients whose disease is progressing despite treatment. We do not know this for sure until we perform an imaging scan at 2 months, however, so in the meantime we reduce the drug dose. The 40% to 50% of patients who have clinically meaningful benefit from regorafenib tend to experience less fatigue.

**H&O** Are there any differences between treating patients who have CRC vs those who have HCC or GIST when it comes to regorafenib?

**TBS** The toxicity profiles with regorafenib are a little bit different among these patient groups. Patients with HCC are eligible for regorafenib only after they have taken sorafenib, which means that they already have experience with a tyrosine kinase inhibitor and have learned some lessons about how to manage similar adverse events. As a result, regorafenib studies show less toxicity in patients with HCC than in patients with CRC. Although HCC is a more challenging form of cancer than CRC given the baseline liver compromise for most, the patients with HCC do surprisingly well on regorafenib.
Patients with GIST take regorafenib in the third-line setting, after imatinib and sunitinib. Because sunitinib treatment is quite toxic, regorafenib treatment may be smoother than expected by comparison.

We have seen this with other agents, given patients’ experience with the toxicity profile, and we are seeing it with regorafenib—patients and physicians have a learning curve when it comes to managing toxicities, so moving on to a new but similar agent leads to fewer toxicities. The experienced patients are better able to muscle through the treatment.

H&O How do you manage other toxicities seen with regorafenib?

TBS We sometimes see hypertension, which most practices know how to manage well. We also see diarrhea, which patients who have CRC and HCC are usually very good at managing following their experience with targeted or chemotherapy regimens.

H&O Is there anything you would like to add?

TBS We monitor liver function very carefully because of the black box warning regarding hepatotoxicity. Some patients will have elevated liver function tests, and in rare cases patients will experience liver failure, which is devastating. I think the key, again, is to keep a close eye on patients.

Disclosure
Dr Bekaii-Saab is a consultant for Bayer, and all fees go to his institution.

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