The Role of Regorafenib in Hepatocellular Carcinoma

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**G&H** What is the mechanism of action of regorafenib?

**CF** The mechanism of action of regorafenib (Stivarga, Bayer) is very similar to that of sorafenib (Nexavar, Bayer). They are both oral multikinase inhibitors. Essentially, they block tyrosine kinases that are very active in angiogenesis, cancer development and growth, and maintenance of the tumor microenvironment. Sorafenib and regorafenib block similar kinases, but regorafenib has more activity against the vascular endothelial growth factor receptors. Regorafenib also is a stronger inhibitor of c-KIT compared with sorafenib and partially blocks TIE2, which sorafenib does not do. This molecule is also important in angiogenesis, potentially allowing regorafenib to be a stronger inhibitor of angiogenesis than sorafenib.

**G&H** Which patients with hepatocellular carcinoma are eligible for treatment with regorafenib?

**CF** The study that brought regorafenib to the forefront of hepatocellular carcinoma (HCC) treatment was the RESORCE (Regorafenib After Sorafenib in Patients With Hepatocellular Carcinoma) trial. Regorafenib is the first second-line treatment that has been shown to have any activity in HCC that has failed to respond to sorafenib. The patients who were eligible for the RESORCE trial had been on sorafenib and were able to tolerate at least 400 mg of sorafenib per day for at least 20 of the last 28 days of their treatment, and had shown documented radiologic progression during their sorafenib treatment. The patients had to be randomly assigned to regorafenib within 10 weeks of their last sorafenib dose, so there was a relatively short interval between treatments.

Almost all of the patients in this study were Child-Pugh class A, and approximately one-third had macrovascular invasion. Approximately 70% had extrahepatic spread (ie, fairly advanced disease). Seventy-five percent of patients were cirrhotic. Most patients were male, with an average age in the mid-60s. The RESORCE trial was a worldwide study, so there were patients from Asia, Europe, the United States, Latin America, and other areas. Alcohol (24%) and hepatitis B virus (38%) were the predominant etiologies behind the HCC of the patients, with hepatitis C virus in another 21%.

**G&H** What were the findings from the RESORCE trial?

**CF** The RESORCE trial included 573 patients whose HCC had previously failed to respond to sorafenib treatment. These patients were randomly assigned 2:1 to supportive care plus either regorafenib or placebo. Regorafenib treatment consisted of cycles of 3 weeks on the agent and then 1 week off of it, unlike sorafenib dosing, which is continuous. Regorafenib improved overall survival, with a median survival of 10.6 months compared with 7.8 months for patients who were on placebo. This result had a hazard ratio of 0.62 and was highly statistically significant. Upon stratification of patients into subgroups, regorafenib was shown to have a benefit regardless of age, extrahepatic disease, macrovascular invasion, and underlying disease, among other factors.

In addition, progression-free survival was 3.1 months with regorafenib vs 1.5 months with placebo. Time to
progression was 3.2 months with regorafenib vs 1.5 months with placebo. Disease control with regorafenib was considered good compared with other agents in second-line trials.

Other findings included partial response, which was seen in 10% of patients, and complete response (according to Modified Response Evaluation Criteria in Solid Tumors), which was seen in 0.5% of patients. In addition, 54.4% had stable disease, and the overall disease control rate was approximately 65%. Interestingly, these data differ from sorafenib data, in which few patients experienced a response. Sorafenib stabilizes the disease, and the response with sorafenib is considered to be stable disease.

G&H Have there been any other studies on regorafenib in patients with HCC?

CF The RESORCE trial is the main study on regorafenib in HCC. Several phase 2 studies have shown very similar numbers. In one phase 2 study, the overall survival of patients whose disease had failed sorafenib treatment and were administered regorafenib was 13.8 months.

G&H What are the most common adverse events associated with regorafenib?

CF The adverse event (AE) profile for regorafenib is somewhat similar to that seen with sorafenib as well as all of the other tyrosine kinase inhibitors. In the RESORCE trial, hand-foot skin reaction occurred in approximately 50% of patients on regorafenib, although only approximately 13% of these reactions were severe. Fatigue occurred in approximately one-third of patients. Hypertension occurred a little more often with regorafenib than with sorafenib; 23% of patients taking regorafenib experienced any grade of hypertension, whereas hypertension is seen in approximately 10% of sorafenib-treated patients. There was also an increase in the bilirubin level with regorafenib, which is also seen with sorafenib because of inhibition of the UGT1A1 transport mechanism for bilirubin. With regorafenib, there was also a small amount of anemia and thrombocytopenia and a small risk of elevated aspartate transaminase (AST) and alanine transaminase (ALT) levels. In the RESORCE trial, these increases were seen in approximately 10% of patients. Because of this, it is recommended that patients be monitored with laboratory tests every 2 weeks for the first 2 cycles of therapy. Finally, there was a small increase in diarrhea with regorafenib, although not as much as with sorafenib.

G&H How can these AEs be managed?

CF Hand-foot skin reaction caused by regorafenib is managed very similarly to how sorafenib-induced hand-foot skin reaction is managed (ie, aggressive moisturizing). I usually have patients start using a moisturizer even before they start the drug and then use the moisturizer twice a day. If they have any sign of hand-foot skin reaction, I switch them to a stronger urea-based cream and instruct them to avoid anything that is hard on their hands and feet, such as uncomfortable shoes and hot water.

Fatigue can be managed symptomatically. I usually recommend that patients plan activities around times of the day when they have more energy, such as in the morning. They also can use caffeine if desired and may need to plan naps. Occasionally, medications, such as armodafinil, are used to help fatigue, although they are rarely necessary and can increase the risk of hypertension.

To manage hypertension, I ask patients to use a blood pressure cuff to monitor their blood pressure at home and call me if it is elevated. Fortunately, most patients with end-stage liver disease have a relatively low blood pressure to begin with, so hypertension is generally relatively easy to control. If patients develop hypertension, it can be controlled with standard antihypertensive therapy.

It is important to monitor AST and ALT levels while patients are taking regorafenib. If the elevations are mild, therapy can be continued. If the elevations are severe (≥5 × the upper limit of normal), therapy may have to be stopped.

G&H How soon do these AEs occur after the initiation of therapy?

CF Interestingly, AEs associated with regorafenib start sooner than those associated with sorafenib. With sorafenib, AEs occur 2 to 6 weeks after the initiation of therapy. In contrast, AEs associated with regorafenib occur at approximately 1 to 2 weeks of treatment. Therefore, it is important to follow up with patients on regorafenib earlier than with those on sorafenib or other multikinase inhibitors. I usually see patients back in the clinic 1 to 2 weeks after starting therapy. Aggressive AE management is important with all multikinase inhibitors because it leads to improved tolerability and longer duration of therapy.

G&H Can regorafenib be dose-reduced?

CF The recommended dose is 160 mg per day (4 pills of 40 mg per day). The package insert and the RESORCE trial include recommendations regarding dose reduction for tolerability. In the trial, approximately half of the patients were dose-reduced and still saw a benefit. The mean daily dose in the trial was 144 mg, but doses ranged from 80 mg to 160 mg. The trial showed that it is possible to dose-reduce regorafenib and still experience an effective antitumor effect; therefore, if patients are having
significant AEs, it is reasonable to dose-reduce the drug. Having the planned 1-week break in the regorafenib treatment cycle also helps tolerability.

**G&H** Are there any difficulties with dose reescalation?

**CF** When the dose of regorafenib is escalated after having been reduced because of AEs, some patients will experience recurrence of their AEs whereas others will be able to tolerate the dose reescalation without significant recurrence of side effects. I try to dose reescalate whenever possible and titrate up and down to find the patient’s maximum daily dose that is tolerable. Finding the maximum dose that the patient can tolerate will keep the patient on therapy longer than trying to force the patient to take a very high dose that he or she cannot tolerate.

**G&H** Are there any other interesting findings regarding regorafenib from the RESORCE trial?

**CF** One other interesting finding was that regorafenib was better tolerated in patients with HCC, according to the AE profile, than in studies of the agent in patients with colon cancer. Regorafenib has been used (and approved) for colon cancer for some time. In this population, patients taking regorafenib can have relatively significant AEs and may have issues with AE management and drug tolerability. The difference in patient reaction may be attributed to the fact that patients in the RESORCE trial were already known to tolerate a tyrosine kinase inhibitor (sorafenib).

**G&H** Are there any special considerations that should be kept in mind when managing patients taking regorafenib?

**CF** It is important to have multidisciplinary discussions whenever possible. Multiple studies have shown that multidisciplinary treatment of HCC will result in better outcomes, as opposed to any one person taking care of these patients. Currently, one of the difficulties when using systemic therapy for HCC is deciding when a patient is failing sorafenib and when the patient should be moved to the next systemic therapy. It is also difficult to determine when to move from locoregional therapy or chemoembolization, for example, to systemic therapy. Multidisciplinary discussion and evaluations can be very helpful in all of these situations.

**G&H** Is regorafenib being examined for approval of an HCC indication?

**CF** A supplemental new drug application has recently been submitted to the US Food and Drug Administration (FDA) and has been granted expedited status. This means that there should be a response from the FDA within 6 months regarding an HCC indication.

**G&H** What are the next steps in research?

**CF** More information is needed on when to switch from sorafenib to regorafenib, which is an important issue. Also important is finding out whether using this drug in combination with other systemic therapies or locoregional therapies can result in better outcomes for the patient. More research is also needed on dose reduction and how much patients experiencing AEs need to take to see a benefit. In addition, there should be research on whether regorafenib can be used in patients who could not tolerate sorafenib. To date, there has only been phase 3 research on regorafenib in patients with HCC who have tolerated sorafenib. However, there is a subset of patients who cannot tolerate sorafenib, so it is important to determine whether regorafenib is a therapeutic option that could potentially be tolerated in these patients or whether that entire class of drugs is not an option because of AEs.

Dr Frenette serves on the speakers bureau, is a consultant, and has been on an advisory board for Bayer Pharmaceuticals.

**Suggested Reading**


