HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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Review of Regorafenib for the Treatment of Hepatocellular Carcinoma

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G&H Why was there a need for a new hepatocellular carcinoma treatment before regorafenib?

RF For the past 10 years, only 1 drug has shown activity for the treatment of advanced hepatocellular carcinoma (HCC), sorafenib (Nexavar, Bayer). This drug was approved in 2007 based on data from the SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol) study, which was a frontline study of patients with newly diagnosed advanced HCC who were randomized to sorafenib or placebo. Placebo was the benchmark at the time because nothing else had been shown to definitively improve outcomes, specifically survival.

After sorafenib, there were no real advances in frontline therapy for many years. Several drugs were examined, but they all had negative findings. In addition, there was a significant unmet need in second-line therapy for patients who progressed after being on sorafenib. There were no therapeutic options for these patients, and although many agents had been evaluated, none had shown activity in a second-line setting either.

Therefore, the RESORCE (Regorafenib After Sorafenib in Patients With Hepatocellular Carcinoma) study evaluating regorafenib (Stivarga, Bayer) was significant because it was the first positive phase 3 study in advanced HCC for nearly a decade and it was the first positive study in the second-line setting. For the first time, there were positive data for a drug after sorafenib that improved survival for patients who had progressed.

G&H Currently, what are the indications for regorafenib?

RF Regorafenib is indicated for patients who have radiographic progression while being on sorafenib. The RESORCE trial only looked at patients who had Child-Pugh A liver disease and had tolerated a minimum dose of sorafenib (to show documented progression). Patients who were intolerant of sorafenib were excluded.

G&H How exactly is progression defined?

RF The challenge with HCC is that all patients have underlying liver disease (ie, cirrhosis), so progression can be clinical (worsening of liver function) or radiographic (based on tumor size). Sorafenib historically has a very low response rate, close to zero, in terms of real tumor shrinkage. Thus, part of the challenge in the frontline setting is how to determine whether sorafenib is working. This clearly has implications for the transition to second-line treatment. Specifically, the RESORCE trial had a radiologic requirement for patients to have progression on sorafenib as per the Response Evaluation Criteria in Solid Tumors—either a new lesion or growth of at least 20% of preexisting disease. Patients on sorafenib are typically imaged regularly while on treatment, and even small changes in size eventually add up. With this definition of progression, patients are not approached when they are clinically progressing, as they are progressing because of declining liver function and it is difficult to help them. However, if patients can be identified before they have

clinical decompensation, when they have documented radiographic progression, that would be an appropriate time to change to a new treatment.

G&H What was the study design of the RESORCE trial?

RF RESORCE was a global, randomized, double-blind, placebo-controlled study of regorafenib, given at 160 mg daily for 3 weeks with 1 week off therapy, vs matched placebo. Inclusion criteria included Child-Pugh A liver function and prior exposure to sorafenib for a minimum period of time with documented progression. Patients were randomized 2 to 1 to regorafenib vs placebo.

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It should be pointed out that this study had 5 stratification factors. This was done because of earlier negative phase 3 second-line studies from which we learned that high α-fetoprotein levels are associated with worse outcomes; thus, it is important to stratify patients for this factor, as well as to separate macrovascular invasion from extrahepatic spread. These 2 groups are often lumped together, but in the RESORCE study, they were separated because each has a different prognostic implication.

G&H What were the key study findings?

RF The primary endpoint was overall survival, and there were several secondary endpoints. Overall survival improved by approximately 3 months, from 7.8 months with placebo to 10.6 months with regorafenib (hazard ratio, 0.63). This is a 37% decrease in the risk of death, which is clinically meaningful. The drug also increased time to progression and progression-free survival, which were key secondary endpoints.

Tolerability of the drug was not too dissimilar from sorafenib in the frontline setting. There had been some concern regarding tolerability because regorafenib is not tolerated as well in patients with colon cancer, but patients in the RESORCE trial tolerated the drug better than the colon cancer population.

G&H Was quality of life measured in this study?

RF Quality-of-life measurements were obtained, including the FACT-G (Functional Assessment of Cancer Therapy–General), FACT-Hep (Functional Assessment of Cancer Therapy–Hepatobiliary), EQ-5D (EuroQol 5 dimensions questionnaire), and EQ-VAS (EuroQol visual analogue scale). There were no clinically meaningful differences between regorafenib and placebo in regard to these measures, which is reassuring given the side-effect profile of the study drug.

G&H What were the limitations of this study?

RF As with other studies of HCC, the RESORCE trial concentrated only on patients who had good liver function (ie, Child-Pugh A status). It is not clear how generalizable the study findings are to a general, non–Child-Pugh A population. Child-Pugh B patients, a large group of patients, may also be reasonable candidates for this treatment, as the liver function of these patients is not that bad, but any overall survival benefit has not been shown. In contrast, Child-Pugh C patients are clearly not candidates for regorafenib owing to their bad liver function. Therefore, it may be reasonable to exercise some judgment as far as recognizing the lack of data in these patient groups and understand that many Child-Pugh B patients have acceptable liver function for some period of time and, thus, may be reasonable candidates for this treatment as well.

Another limitation is that the study required patients to tolerate sorafenib for a certain period of time. Some patients do not tolerate sorafenib well at any dose. One of the reasons that patients had to have a history of tolerating sorafenib while having progression is because the natural history of progression on sorafenib is already known, and a patient who is sorafenib-intolerant would be considered as part of the frontline population, not the second-line population. It is unclear how well patients who are sorafenib-intolerant would tolerate regorafenib and what the true efficacy is in that group. In addition, we do not know if the tolerability of regorafenib is the same in a patient who did not tolerate sorafenib.

G&H Why did patients in the study benefit with regorafenib when their disease had progressed on sorafenib, which is similar? How different are these agents?

RF The 2 agents are similar but do have their differences. Regorafenib has a kinase profile that is a little different than that of sorafenib; regorafenib also has a target profile that is a little broader. Regorafenib seems more potent

than sorafenib for some targets that they both hit as well. However, although both regorafenib and sorafenib are multikinase inhibitors, their mechanisms of action in tumor tissue are not completely clear. Nevertheless, we do know that both improve survival, which is very important.

The other difference between the 2 agents is the response rate. At least in second-line treatment, regorafenib has a higher response rate than that seen with sorafenib in the frontline setting. This may be because the molecules are different.

G&H Have there been any other observations from the RESORCE trial?

RF At the 2017 Gastrointestinal Cancers Symposium, my colleagues and I presented findings from another analysis of the RESORCE trial. We looked at the time of death (from the start of sorafenib until death during the study). Overall survival was up to 26 months in these patients. These findings are not generalizable, as they occurred in a select trial population. However, 26 months survival for the sequence of sorafenib to regorafenib and death on study can be used as the benchmark for future studies.

In addition, other analyses from the RESORCE study, as well as other work from Dr Jordi Bruix and colleagues, have shown that progression outside the liver carries a worse prognosis than progression inside the liver. This is an interesting concept because many people assume that progression in the liver is worse, but that location is not always associated with worse outcomes.

As for future analyses of the RESORCE trial, work is currently being conducted to try to identify biomarkers that might determine which patients would do better than others with regorafenib.

G&H Thus far, does it seem that the real-world experience of regorafenib matches the clinical trial data?

RF HCC is a difficult disease, and the challenge is that patients in a clinical trial are highly selected with strict inclusion and exclusion criteria, although that is the case with every clinical trial. Regorafenib was approved only in April of this year, so there is not yet much real-world experience with it, but I expect that for patients in the real world who are well compensated and have progressed on sorafenib, results will be similar to those from the trial. There likely will be some differences, as real-world treatment is an uncontrolled experience, but as has been seen with sorafenib, real-world experience tends to mimic clinical trial experience, at least in my own patients. I think that regorafenib will eventually become the standard of care.

G&H How frequently should patients be monitored while on regorafenib?

RF When I start my HCC patients on systemic treatment, I usually see them back within 2 weeks to make sure they are tolerating therapy. Until they are stable, I see them every 2 weeks, and then seeing them monthly at the beginning of each cycle would probably be reasonable. Being proactive to manage side effects is important to keep patients on treatment and minimize morbidity.

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In terms of monitoring the disease itself, patients should undergo imaging on a regular basis, probably every 2 months or so to make sure that the disease is under control.

G&H Overall, how safe and tolerable is this agent?

RF It is certainly safe. We did not see a high number of grade 5 adverse events or anything that is associated with death. Regorafenib has many of the adverse effects that have been seen with sorafenib, such as hand-foot skin reaction, diarrhea, and hypertension, but by now doctors who treat patients with advanced HCC should be comfortable managing these adverse effects.

G&H How are these adverse effects usually managed?

RF Seeing patients regularly is important. Even though regorafenib is an oral drug, it still needs to be managed like other anticancer agents. I cannot stress enough how important it is to see patients early and regularly to help mitigate toxicity before it becomes a bigger problem. For hand-food skin reaction, management can include topical emollients, urea-based creams, and the wearing of comfortable shoes. For diarrhea, patients should be proactive and have aids such as loperamide readily available. For hypertension, nearly any antihypertensive

agent can be used, such as calcium channel blockers or beta blockers, and dose interruptions and reductions of regorafenib should be considered if these efforts are not successful.

G&H When else should the dose of regorafenib be reduced?

RF If the patient cannot be managed supportively (eg, if the patient is having grade 3 adverse effects that cannot be managed), then dose reductions would be appropriate. Grades of adverse effects can be difficult to determine, however. Thus, physicians should use their clinical judgment as to when the dosage should be reduced. For example, if a patient is losing a lot of weight and having a lot of diarrhea despite using loperamide, dose reduction would be a good idea. Likewise, if a patient has bad hand-foot skin reaction that is interfering with his or her daily activities despite optimal management, then that patient should be dose-reduced as well.

Dose escalation can always be considered if the patient's adverse effects become controlled. However, in my experience, dose escalation is not common because most adverse effects tend to recur.

G&H What future research is needed to improve the efficacy of HCC treatment, specifically regorafenib?

RF More effective treatment is still needed. The challenge has been in identifying therapies that are better than sorafenib in the frontline setting. Perhaps a combination strategy of regorafenib and immunotherapy agents could be fruitful. I would not rush to assess the drug in combination with chemoembolization or in earlier-stage disease, as the efforts with sorafenib were not very successful.

In addition, it is important to better identify which patients are appropriate candidates for systemic treatment. There is a tendency for patients who have liver-confined disease to continue to undergo locoregional therapies such as chemoembolization, but those types of procedures can induce liver damage and can prevent patients from being candidates for effective systemic treatment. With the approval of regorafenib, we now have a continuum of frontline and second-line treatment, so it is important to recognize which patients have advanced disease. If they are progressing on locoregional therapy, they should start systemic treatment before they are too sick to do so because there is a limited window of opportunity to use all of these treatments. If patients are not offered systemic treatment when they have preserved liver function, they may miss the opportunity to receive a treatment sequence that is proven to extend survival.

Dr Finn is a consultant for Bayer.

Suggested Reading

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