HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

Section Editor: Robert G. Gish, MD

Treatment of Intermediate-Stage Hepatocellular Carcinoma

Richard S. Finn, MD
Associate Professor of Medicine
Department of Medicine, Division of Hematology/Oncology
Geffen School of Medicine at UCLA
Los Angeles, California

G&H What defines intermediate-stage hepatocellular carcinoma?

RF Several systems have been implemented for staging hepatocellular carcinoma (HCC), the most common of which is the Barcelona Clinic Liver Cancer (BCLC) staging system. In this system, patients with HCC are defined as having very–early-stage (stage 0), early-stage (stage A), intermediate-stage (stage B), advanced-stage (stage C), or terminal-stage (stage D) disease. Patients who are intermediate-stage—BCLC stage B—typically have a good performance status and often have preserved liver function. They also have multifocal HCC within the liver (ie, confined to the liver without vascular invasion or extrahepatic spread), however, so these patients are usually not candidates for surgical resection.

G&H How is intermediate-stage HCC usually managed?

RF The main treatment approach is typically chemoembolization because these patients have multifocal disease and good performance status, and chemoembolization has been shown to improve survival in this patient population. Two randomized studies as well as a meta-analysis have confirmed the benefit of transcatheter arterial chemoembolization (TACE) in this population. There may be a subset of patients with intermediate-stage disease who can be considered surgical candidates (ie, multifocal disease in only 1 lobe might be amenable to surgical resection).

Currently, there are various methods of performing chemoembolization, such as with the use of ethiodized oil (Lipiodol, Guerbet) or doxorubicin-loaded beads. More recently, the catheter-based approach of radioembolization has been considered in this group of patients. While we are still learning about the role of radioembolization in this patient population, the procedure does appear to be safe, although there are no strong efficacy data to support the idea that radioembolization is superior to chemoembolization.

G&H Are any patients with intermediate-stage HCC eligible for sorafenib therapy?

RF Sorafenib (Nexavar, Bayer/Onyx) is an oral tyrosine kinase inhibitor that blocks the activation of the vascular endothelial growth factor (VEGF) receptor as well as other kinases, and it is the only agent that has been proven to extend survival in advanced HCC. Typically, the patients who are being treated with sorafenib are those who have BCLC stage C disease, which is defined as symptomatic HCC, typically with vascular invasion and/or extrahepatic spread or HCC that is affecting their performance status. In addition, their Child-Pugh score tends to be lower.

The patients with intermediate-stage disease who would be candidates for sorafenib therapy are those in whom local ablative approaches (typically chemoembolization) are not controlling the disease. For example, there are patients who are chemoembolized several times, and at some point the tumor stops responding to the chemoembolization and

continues to grow. These are patients who might still be classified with intermediate-stage HCC because they do not have vascular invasion or extrahepatic spread. Even though these patients do not have BCLC stage C disease, it would be appropriate to offer them sorafenib therapy. In all of the phase 3 studies looking at sorafenib vs placebo or sorafenib vs other systemic agents, approximately 15% of the patients have BCLC stage B disease that has progressed after chemoembolization. Retrospective data from the SHARP (Sorafenib HCC Assessment Randomized Protocol) study demonstrated a hazard ratio of 0.72 for overall survival for this group of patients, consistent with the benefit seen in the overall population.

The bigger question is whether there is a role for sorafenib in patients who have intermediate-stage disease that has not progressed on chemoembolization. Several studies have looked at sorafenib in combination with chemoembolization or sequentially after chemoembolization, and none of those studies have shown any benefit to moving sorafenib earlier in the course of therapy. To be clear, patients who have BCLC stage B disease that progresses on chemoembolization certainly do receive a benefit from sorafenib therapy. However, in other intermediate-stage patients, local ablative therapies such as TACE should be exhausted before moving on to sorafenib therapy.

G&H Could you further discuss the use of sorafenib in combination with locoregional therapy in the intermediate stage of HCC? What is the rationale for investigating this combination?

RF Several studies have looked at the role of sorafenib in intermediate-stage HCC. All of these have examined chemoembolization plus sorafenib or chemoembolization alone, and the timing of sorafenib around TACE has varied from study to study. I think that we can conclude from these studies that sorafenib can be combined safely with TACE; however, as mentioned above, there is no therapeutic benefit to doing this.

The rationale for using an agent such as sorafenib with chemoembolization is that chemoembolization induces ischemia to the tumor in the liver, and ischemia is a potent inducer of VEGF secretion. This has been hypothesized as one of the reasons that chemoembolization fails; even though tumor necrosis is being induced to part of the tumor, VEGF rises and other growth factors stimulate tumor growth. Therefore, the rationale has always been that if a drug such as sorafenib is given around the time of the chemoembolization, this theoretical tumor stimulation effect could be controlled and outcomes could be improved. As it turns out, sorafenib can be used safely in the perioperative chemoembolization period, but it has no benefit in this setting. Patients on TACE and sorafenib did just as well in terms of overall survival or time to progression as those who received chemoembolization alone. The SPACE (Sorafenib or Placebo in Combination With Transarterial Chemoembolization [TACE] With Doxorubicin-Eluting Beads [DEBDOX] for Intermediate-Stage Hepatocellular Carcinoma [HCC]) study was one of several randomized studies that attempted to show a benefit.

G&H Do response rates correlate with overall survival with locoregional therapy?

RF This is a very important question. As we have seen in prospective studies, tumor response in the context of systemic treatment is not necessarily correlated with outcome. There has been an effort to move away from conventional assessments of tumors, such as the Response Evaluation Criteria in Solid Tumors (RECIST) criteria that look just at the size of the tumor seen on imaging, to concentrating more on the contrast-enhancing component of the tumor. The development of modified RECIST (mRECIST) criteria is an effort to capture these treatment effects. Those types of assessment criteria have been used in the intermediate stage, where chemoembolization has been used for some time, and this loss of enhancement after the procedure is common. For example, the European Association for the Study of the Liver criteria have been used, which take into account the amount of enhancement of the tumor after an embolization procedure. The sense is that in an intermediate-stage HCC, those types of responses do correlate with better outcomes.

G&H What are the most common adverse events associated with sorafenib therapy in this setting?

RF There are no unique adverse events from using sorafenib specifically in the setting of intermediate-stage HCC. Sorafenib does have known toxicity (most predictably gastrointestinal toxicity and skin) and adverse effects such as diarrhea, painful hand-foot skin reactions (which are manageable), hypertension, and fatigue, but these are common regardless of the stage of the patients being treated.

G&H Are any other systemic options available for patients with intermediate-stage HCC?

RF There is currently no systemic agent being used in intermediate-stage HCC, but there have been several studies of systemic agents in combination with TACE. Most noticeably, there was a very large study of the investigational agent brivanib, but because the agent did

not end up having any activity in advanced disease, the early-stage disease study was stopped early, even though in some subgroups there was perhaps an advantage in extending time to progression. Studies with other agents have all been negative, as well.

One interesting systemic agent being investigated in intermediate-stage HCC is ThermoDox (Celsion), a heat-activated formulation of doxorubicin designed to increase the amount of tumor killed with radiofrequency ablation. A study is currently comparing patients who are receiving radiofrequency ablation alone or in combination with ThermoDox.

G&H What are the next steps in research in this area?

RF There are several areas that require improvement. TACE does extend survival (with survival possibly reaching up to 3 years in this group of patients), but it would be good to have an agent that could be used as an adjuvant to TACE that could improve survival as well as disease control. Currently, there is no such agent. Hopefully, we will have a more active agent in advanced disease, and then that would offer the opportunity to evaluate the agent in earlier-stage disease. Currently, radioembolization is providing some excitement, as it appears to be a promising new technique. It has a slightly different side effect profile than chemoembolization, but randomized data are needed to determine whether it is more efficacious than chemoembolization.

Dr Finn has been a consultant to Bayer and Bristol-Myers Squibb.

Suggested Reading

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