

# HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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## Hepatocellular Carcinoma: Current Questions and Future Directions



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**G&H** How are liver organs allocated to patients with hepatocellular carcinoma, and are any changes expected to this system over the next several years?

**RG** One of the biggest controversies in hepatocellular carcinoma (HCC) and organ allocation is that patients with HCC have been receiving liver organs ahead of, or preferentially to, patients who were dying of liver failure from other causes. The allocation system is supposed to have parity; people with the same risk of dying are supposed to have the same access to organs.

There have been 2 recent proposals to correct this HCC “advantage” for organ allocation. The first proposal is to provide a ceiling for Model for End-Stage Liver Disease (MELD) points so that a patient with HCC can receive a maximum of 34 points. This change would most affect patients and centers with long waiting times, particularly those in large cities and coastal regions, which often have many patients listed for transplantation and a predominance of patients with MELD scores greater than 34 points.

The other proposal is to have a 6-month watch-and-wait period for patients with HCC. For example, if a patient with HCC is placed on the liver transplant list with an HCC MELD score of 22, he or she would become inactive for 6 months with the HCC MELD points, and then would become active as a liver transplant candidate with a MELD score of 27 and be eligible for organ allocation.

There are 2 reasons for using a 6-month inactive period. One is that some centers use low MELD scores (in the 20s) for liver transplant because of geographic disparities in organ allocation, so this change would prevent those patients from receiving organs for their HCC MELD scores until their MELD scores increase to 27. I believe that this change would help re-equilibrate organ distribution and allocation to be compliant with the 1998 Final Rule from the US Department of Health and Human Services to make sure that organ allocation is not based on accidents of geography. The second reason for having an inactive period for 6 months is to detect aggressive cancers. Some patients will develop metastatic disease, vascular invasion, or other contraindications to liver transplant during this inactive period, and they should not be allocated an organ.

Over the next year, both of these proposals will likely be adopted to improve the liver organ allocation system. The next potential issue is whether patients with small lesions who achieve complete ablation with liver-directed therapy should receive MELD exception points in the absence of imaging evidence of HCC.

**G&H** How will the Liver Imaging Reporting and Data System be incorporated in radiology reporting?

**RG** The Liver Imaging Reporting and Data System (LI-RADS) has been working in parallel with the scoring

system of the Organ Procurement and Transplantation Network (OPTN), which is used by the United Network for Organ Sharing (UNOS). The OPTN's scoring system counts the number and size of lesions, but it has a slightly different terminology than LI-RADS.

Over the past 2 years, a working group has been trying to bring the 2 terminologies together as close as possible. LI-RADS is a general scoring system of the probability of HCC in patients who have cirrhosis or other patients at risk for HCC; this system is not meant to be used in random tumors that might be found in a liver scan, such as when a patient is undergoing a scan as part of an appendix workup or abdominal pain evaluation. In its first generation, LI-RADS was not meant to be used just for liver transplant and organ allocation.

However, because LI-RADS is now being used nationally at many centers—it is becoming the standard of care for scan interpretation in my opinion—it is very important that LI-RADS be as close to the OPTN's scoring system as possible so that when doctors in the community are scoring liver tumors, transplant centers can use that information for UNOS applications for HCC MELD points and obviate the need for repeat scanning.

### **G&H** Is liver biopsy still important in the management of HCC, and will it be in the future?

**RG** I believe that HCC liver biopsies will become the standard of care in the next few years for most patients with HCC. This is because HCC will become similar to breast or lung cancer, in that the characteristics of the tumor (ie, the receptors or signaling that takes place in the tumor) will help drive the choice of anticancer chemotherapy or, more importantly, what we now call targeted therapy.

An example is the experimental medication tivantinib. To be eligible for the tivantinib trial, patients had to have a high expression of c-MET—one of the oncogenes involved in cancer formation, stimulation, and so on—in their liver tissue. If this trial has positive findings (ie, if the biopsy results lead to better treatment and response rates), it will break ground in the HCC world for other trials. In addition, positive findings would cause the US Food and Drug Administration (FDA) and pharmaceutical companies to start viewing HCC as a more heterogeneous disease that may have 5 to 10 different dominant signaling pathways that are part of the initiation and propagation of the HCC tumor and subsequently are targets for drug therapy.

Therefore, we should encourage our radiology and surgical colleagues to biopsy tumors early, before interventions take place, in order to obtain unadulterated and uncontaminated tissue. This biopsy information should also be very useful for determining the prognosis of patients with HCC.

### **G&H** Are there any significant risks associated with liver biopsy in these patients?

**RG** The main risk of needle core liver biopsy is seeding cancer cells along the needle track that may show up clinically in a patient at a later date. Most doctors believe that the risk of seeding is less than 3%, but many studies are now reporting that the risk is far less than 1%. This risk depends on proper biopsy technique, the skills of the radiologist, and the device used for the biopsy. A 2-stage biopsy approach can be used to minimize the likelihood of dragging tumor cells along the needle track.

The other potential risk of liver biopsy is bleeding from the site of the biopsy, but this is a rare event (<1% of cases). There are also several contraindications to performing liver biopsy, such as the presence of ascites and poor anatomic location (eg, being near a blood vessel, which might predispose the patient to bleeding).

### **G&H** How is sorafenib currently being used in clinical practice? Which patients benefit from treatment with this drug?

**RG** Sorafenib (Nexavar, Bayer/Onyx) is indicated for patients who have HCC that is unresectable either because of its size or location in the liver or because patients have a primary tumor in the liver that is metastatic or multicentric.

There was some controversy recently because the SPACE trial and preliminary reports from the SPARE trial seemed to suggest that combination therapy of sorafenib and transarterial embolization or surgery has not yet come to be standard of care. With sorafenib alone, the prolongation of life was approximately 2.1 and 2.8 months in the AP and SHARP trials, respectively, in patients who received sorafenib vs those who received placebo. This led people to conclude that sorafenib added only approximately 3 months of life.

However, that is not how the data should be interpreted. Both of these studies were stopped by the Data and Safety Monitoring Board because the survival difference was so statistically large at approximately the 30-month point that the investigators could no longer ethically continue administration of placebo. Therefore, the survival difference between sorafenib and placebo is, at a minimum, 2.1 to 2.8 months and probably would have been much larger if the investigators had been able to continue the study.

In my clinical experience, approximately one-third of patients with HCC receive a profound benefit from sorafenib (ie, extension of life from 6 to 18 months or longer). I have had some patients live as long as 30 months during sorafenib therapy, even with metastatic disease. These patients appear to have sorafenib-sensitive

tumors and have either stable disease or regression of disease on sorafenib. These patients are tolerating sorafenib with a reasonable to good quality of life. My responsibility as a treating physician is to use sorafenib in my patients with unresectable HCC and to find the patients who can tolerate and respond to it.

**G&H** Do you expect any further trials on combined modality treatment approaches for HCC over the next few years?

**RG** Yes. Different centers have been looking at combining sorafenib with bead embolization, chemoembolization, radioembolization, resection, or thermal ablation. Some of the early studies did not show a broad benefit, but there were some populations that did benefit from combination therapy. Studies are now being designed differently to see whether sorafenib can be used with transarterial or thermal ablation with interventions much closer to the time of sorafenib use so that there is no “holiday” off drug.

I do believe that there is a role for this combined therapy, but we do not yet know its exact role, and we need studies that are appropriately designed.

**G&H** What are the drugs currently in development for HCC?

**RG** There are a large number of drugs currently being developed for HCC, such as sunitinib (Sutent, Pfizer), brivanib, linifanib, ramucirumab (Cyramza, Eli Lilly), bevacizumab (Avastin, Genentech), cediranib, pazopanib (Votrient, GlaxoSmithKline), and lenvatinib (Lenvima, Eisai). HCC is the second-leading cause of cancer death in the world, and there are between 600,000 and 1 million new HCC cases in the world annually, so this is clearly still an important area for basic science, clinical science, and drug development.

Despite much money and research, only one drug, sorafenib, has been approved in the United States or globally for use in patients with HCC thus far. Companies will need to work more closely with the FDA to come up with ways to profile tumors and find the right medication to treat the right patient. This goes back to the discussion earlier about finding receptors and signaling pathways that are dominant, and then using the right medication or combination therapy with tumor biopsy. I look at HCC as a viral disease; many viruses are treated with combination therapy to obtain optimal response from patients, as will HCC.

**G&H** How do the new drugs differ from the existing drugs?

**RG** There are new drugs targeting telomerase, Wnt/ $\beta$ -catenin, and other signaling pathways, as well as

combinations of signaling pathways, such as fibroblast growth factor, vascular endothelial growth factor, and platelet-derived growth factor, all of which are signaling pathways that dominate HCC. The new drugs are targeting either single or multiple sites, and if they are targeting single sites, researchers are looking at combination therapy thoroughly, which is what I consider to be the most exciting option.

**G&H** Why have so many clinical trials failed in the past?

**RG** Many trials have failed because there has been a lack of profiling and targeting of the tumors, now called personalized medicine or treatment. The drugs being studied may have a benefit for only 20% of patients with HCC, yet they are being studied in all patients. All tumors are not equal. Every patient has a slightly different tumor profile. We need personalized medicine to apply the best new technologies to profile tumors and target the right drug to the appropriate tumor.

**G&H** Will  $\alpha$ -fetoprotein and other biomarkers have a role in HCC surveillance in the future?

**RG** I predict that  $\alpha$ -fetoprotein (AFP), as a single biomarker, will eventually re-enter the American Association for the Study of Liver Diseases guidelines for HCC surveillance and for use as a risk marker. It is important that the Lens culinaris agglutinin A-reactive fraction of AFP (also known as AFP-L3%) and des-gamma-carboxy prothrombin also be looked at, not for diagnosis of HCC, but to determine the risk for HCC as well as AFP. These biomarkers have been approved by the FDA as risk markers and can help guide clinicians during surveillance of HCC, although not screening or diagnosis.

We also need more and better biomarker panels. If the tumor is heterogeneous, then the biomarker panel also needs to be multifaceted so that clinicians can assess a patient who may be producing one type of biomarker but not another.

**G&H** Do you agree with the recent Veterans Affairs systematic review that surveillance for HCC is unproven?

**RG** First of all, the systematic review conducted by Kansagara and colleagues used the wrong term in the title and text of their manuscript in my opinion. The authors discussed screening for HCC across the medical literature, but screening is the first test that clinicians use when testing patients for a disease; surveillance indicates ongoing testing and monitoring of a patient at risk for

a disease. The way that the authors termed their paper, surveillance vs screening, set the wrong tone from the beginning because the wrong terminology was used.

Second of all, they looked at a variety of papers from a very high methodologic quality level and eliminated papers that had any type of defect in their study design. The problem is that no researchers are going to conduct a controlled study without screening and surveillance for HCC. Thus, it is impossible to conduct such a study ethically because screening and, more importantly, surveillance are the standard of care in communities throughout the world. It is not possible to decide that although a modality has been used as the standard of care for 20 years, it will no longer be used until a 10-year controlled study has been performed to proven its usefulness. During those 10 years, thousands, if not tens of thousands, of patients would die from HCC.

Most HCC experts believe that surveillance works, which is why we use it, and this has been shown in studies such as a recent one by Pocha and colleagues, which supported the use of biannual ultrasonography for HCC surveillance. The authors found that biannual ultrasonography was marginally more sensitive for the detection of early HCC compared with annual computed tomography, and no control group or patient group without surveillance was included in this study. In addition, this study provides support for continuing to use ultrasonography as the foundation for surveillance instead of exposing patients to unnecessary radiation risk. We need more studies looking at how to determine the right type of surveillance and how to use surveillance with biomarkers.

*Dr Gish receives fees for promotional lectures from Bayer/ Onyx and Wako Diagnostics as well as consulting fees from BTG, which makes drug-eluting beads to treat HCC as well as radiolabeled beads.*

## Suggested Reading

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