The Role of Liver Biopsy in Hepatocellular Carcinoma

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G&H  How close are we to using precision medicine to guide hepatocellular carcinoma treatment?

RF  We are closer than we have ever been before. There has been a lot of molecular work done in hepatocellular carcinoma (HCC) that has identified important pathways and targets for therapy. However, we still have not seen these targets validated the way they have been in other types of cancer. In breast cancer, for example, human epidermal growth factor receptor 2 (HER2) or estrogen and progesterone receptors can be used to make treatment decisions based on drugs targeting those pathways. In HCC, we have seen a number of treatment failures in clinical development, which is spurring researchers to look back more closely and try to get the right drugs to the right patients, based on specific biomarkers. There are several studies currently being conducted that address this therapeutic approach.

G&H  What drugs are in development for HCC in which liver biopsies are guiding or stratifying treatment?

RF  Tivantinib is the drug that is furthest along. This molecule blocks the c-MET protein, which is an extracellular receptor that has been identified as a potential target within HCC. There currently is a study of patients who have received sorafenib (Nexavar, Bayer HealthCare) in the first-line setting of advanced HCC and have experienced disease progression while on the drug. In order to enroll in this phase 3 study, a piece of HCC tumor has to be sent to a central laboratory and immunohistochemistry staining has to reveal an elevated c-MET level; once enrolled, the patient is randomized to receive tivantinib (to specifically block the c-MET protein) or placebo. This study design is based on a phase 2 study in which researchers initially studied all patients and gave them tivantinib, but a real benefit was seen only in those patients who had high c-MET levels in their tumors (a retrospective finding).

G&H  Are there any other HCC drugs in development in which liver biopsies are guiding treatment?

RF  Yes, there are drugs earlier in development. There is a genetic alteration that occurs in a subset of HCC, in which the fibroblast growth factor 19 (FGF19) ligand is amplified. FGF19 signals through a protein called FGF receptor 4 (FGFR4). My colleagues and I have found that certain kinase inhibitors of the FGFR axis are active in tumors that have amplification of the FGF19 gene. Thus, there are a number of molecules in phase 1 development targeting HCC with alterations in the FGF19 and FGFR4 pathways.

There is another therapeutic approach that should be mentioned. The antibody to the vascular endothelial growth factor ramucirumab (Cyramza, Lilly) was studied in patients with advanced HCC after sorafenib therapy. That large phase 3 study had negative results, but when the researchers went back, they saw that patients who had elevated alpha-fetoprotein (AFP) levels in their blood received a benefit from the drug. Therefore, there is now
a new study with this drug that is enrolling only patients who have received sorafenib therapy and have high AFP levels in their blood. This is a biomarker-driven study, but the biomarker is not in the tumor.

In summary, there is now a new generation of biomarker-driven studies in HCC. Some of these studies are requiring biopsy material at inclusion. If these studies are positive, it will become standard procedure to test a patient’s tumor to see if he or she is a candidate for a specific therapy.

G&H Are there any dominant markers or altered pathways that appear to drive HCC?

RF HCC is a very complex disease. We do not think that these cancers are driven by a single alteration—not like chronic myelogenous leukemia, in which there is just one genetic alteration in the BCR-ABL gene that causes the disease. We are looking to validate molecular targets, and the ongoing studies will determine whether this molecular targeting is a valid approach in HCC.

G&H What are the risks of liver biopsy in HCC patients?

RF Several concerns have been raised with liver biopsy in the setting of HCC, and in most cases, a biopsy is not required to make the diagnosis of HCC. There are well-defined imaging criteria for that. One risk is bleeding. Bleeding is a risk for any patient who undergoes a biopsy. However, because HCC patients often have some degree of cirrhosis, they usually have a higher bleeding risk than other patients, meaning that they might have a low platelet count or prolonged clotting time (ie, an elevated international normalized ratio or prothrombin ratio). Nevertheless, even if a patient has a tendency to bleed, liver biopsy can be performed safely, and, if necessary, the patient can receive platelets or plasma.

The other concern that is raised more frequently for liver biopsy and is specific to HCC is seeding of the tumor. If a liver with cancer is biopsied, there is a small risk that as the clinician pulls out the needle, some of the track that the needle passes through will spill tumor cells and lead to tumor spread. However, the clinician can use a trocar and burn the needle track, which makes the incidence of seeding very low (probably less than a few percent at high-volume centers).

G&H When is liver biopsy indicated in patients with HCC?

RF Because of the risks of bleeding and seeding, it is important to make sure that liver biopsy is actually needed in a patient with HCC. For primary HCC, a liver biopsy is often not needed. In the majority of cases, diagnosis can be made with imaging alone. Very clear criteria from the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases define the characteristics of HCC in a patient who has cirrhosis. A lesion in a patient with underlying liver disease that is hypervascular on the arterial phase and has delayed washout can be very specific to HCC, and in this case, does not require a liver biopsy. If a patient has curable HCC and can be diagnosed radiographically, there is no need to obtain a liver biopsy—although in centers with a lot of experience with biopsies, they can be performed and are safe.

It is important to note that liver biopsy is not contraindicated in patients with HCC. In a patient with advanced HCC, the theoretical risk of tumor seeding is not of any significance because the patient already has advanced disease. In this case, if biopsy findings are going to dictate who receives a certain molecular therapy, then biopsy should be performed.

G&H Should patients whose disease has failed to respond to treatment undergo liver biopsy?

RF In the context of research, they should. If a patient needs to undergo liver biopsy to enroll in a clinical trial, there is no contraindication to the procedure, so he or she should undergo biopsy, assuming that the bleeding risk is manageable. At this time, there is no other reason that a patient should undergo a biopsy except for research. If a patient is just going on standard-of-care therapy that does not require a biomarker or does not involve any research questions, I see no reason to put the patient through liver biopsy.

It is also important to note that if a patient has been cured of his or her HCC or has had a liver-only disease that has been controlled, and he or she develops an extrahepatic lesion or metastases, I often advocate that the first occurrence of metastatic disease be confirmed with a liver biopsy.

G&H Is there a role for liver biopsy in HCC treatment with sorafenib and regorafenib?

RF In the front-line setting, there is no indication for liver biopsy. There are no biomarkers or tumor markers that have been associated with more or less benefit from sorafenib. Now, we are seeing activity in the second-line setting with regorafenib (Stivarga, Bayer HealthCare), but just like with sorafenib, there is no biomarker that has been identified of patients who do better or worse with regorafenib treatment. If, for example, the tivantinib
c-MET study has positive results, clinicians will likely start biopsying patients with progression on sorafenib to see whether they qualify for tivantinib treatment.

**G&H** Are liver biopsies needed to guide the use of checkpoint inhibitors?

**RF** There is great excitement in the field regarding the potential for immunotherapy in HCC. This excitement comes mostly from the activity that these drugs have had in other difficult-to-treat diseases, such as melanoma and lung cancer and, recently, bladder cancer and head-and-neck cancer, and that list continues to grow. Some phase 2 data with nivolumab (Opdivo, Bristol-Myers Squibb) look very exciting, showing that the drug has activity in HCC patients, some of whom had prior sorafenib therapy. However, this study was done without preselection for programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) expression. Of the 2 inhibitors that are furthest along, nivolumab and pembrolizumab (Keytruda, Merck), biomarker findings have not been consistent. Whereas pembrolizumab has looked at PD-L1 expression and has associated more expression with more benefit in lung cancer, nivolumab has not necessarily pursued that approach. However, both drugs have approvals for use in various diseases, and both are being studied in HCC. Nivolumab is being studied in the front-line setting vs sorafenib, and pembrolizumab is being studied in the second-line setting vs placebo.

**G&H** Will liver biopsy continue to play a role in HCC in the future?

**RF** Yes, in fact, I think that in the future liver biopsy will play more of a role in HCC. I suspect that some of these targeted approaches will have positive phase 3 study results, and new drugs will be tied to a biomarker. However, for early-stage HCC, I do not know whether there will be a change soon in the role of liver biopsy outside of the research setting.

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

**RF** Many of the ongoing clinical trials are requiring the retrieval of some tissue for retrospective biomarker analysis so that researchers can go back and look at biomarkers because there have been so many therapeutic failures in phase 3 research. I think that we in the field have recognized that we need to do better and try to personalize therapy more when possible, such as connecting targeted drugs with a targeted population of patients. That targeted population can be defined by testing the tumor or blood work, as we hope will be done in the future.

*Dr Finn has served as a consultant to Bayer, Novartis, Pfizer, and Bristol-Myers Squibb.*

**Suggested Reading**


Zhu AX, Park JO, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH); a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2015;16(7):859-870.