Expert Perspectives on Evidence-Based Treatment Planning for Patients With Hepatocellular Carcinoma

Jorge Marrero, MD, Mary A. Maluccio, MD, Heather McCurdy, RN, and Ghassan K. Abou-Alfa, MD

Introduction

Hepatocellular carcinoma (HCC), the most common type of liver cancer, is an aggressive malignancy with a generally poor prognosis (5-year survival rate of 15%), and it can be challenging to treat. Most patients present with advanced-stage HCC not amenable to surgery or transplantation as well as underlying comorbidities, such as liver cirrhosis or chronic hepatitis infection.

The following report presents highlights from a roundtable discussion between 4 leading experts in HCC: Jorge Marrero, MD, from the University of Texas Southwestern Medical Center, Mary A. Maluccio, MD, from the Indiana University Melvin and Bren Simon Cancer Center, Heather McCurdy, RN, from the VA Ann Arbor Healthcare System, and Ghassan K. Abou-Alfa, MD, from the Memorial Sloan Kettering Cancer Center and the Weill Cornell Medical College at Cornell University. The panel members share insights into how they stage and monitor patients, their treatment strategies for early-, intermediate-, and advanced-stage HCC, and promising novel therapies on the horizon. In addition, case studies are used to demonstrate selected therapeutic strategies in real-world scenarios.

Scope of the Problem

Dr Marrero: HCC is a global disease. It is the second most common cause of cancer-related mortality worldwide and is estimated to be responsible for nearly 746,000 deaths in 2012. It is most prevalent in less-developed countries in Asia and Sub-Saharan Africa, where it is correlated with the prevalence of chronic hepatitis B virus (HBV) infection. In the...
United States, the incidence of HCC is increasing, often occurring in patients with chronic hepatitis C virus (HCV) infection; the incidence rates for men and women increased by 3.7% and 2.9%, respectively, from 2006 to 2010 (Fig 1).\(^1\) In 2014, an estimated 33,190 new cases of HCC will be diagnosed in the United States, and 23,000 people will die from the disease.\(^3\) In addition to HBV and HCV infection, risk factors for the development of HCC include alcohol use, fatty liver disease, hereditary hemochromatosis, and cirrhosis from any cause.\(^5\)

**Dr Abou-Alfa:** The increasing incidence of HCC in the United States is a major concern. This increase has been driven by hepatitis C; however, with increased awareness, HCV infections are already on the decline.\(^6\) It is unclear how the approval of sofosbuvir will influence the incidence of HCV-related HCC, although one may speculate that the approval will have a positive impact. Sofosbuvir is an oral nucleotide analog inhibitor of the HCV NS5B polymerase enzyme, which plays an essential role in the replication of HCV. It was approved by the US Food and Drug Administration (FDA) in December 2013 for the treatment of chronic HCV infection as part of a combination antiviral regimen.\(^7\) However, because it takes up to 30 years to develop HCC after HCV infection, the positive impacts of sofosbuvir may not be felt for some time. The primary driver of HCC will then become nonalcoholic fatty liver disease due to morbid obesity and diabetes.

**Dr Marrero:** I think that is a great point, Dr Abou-Alfa. The new antivirals may change the natural history of this disease. However, there is a potential problem. An intervention such as antiviral therapy will reduce the risk of HCC only if everyone is treated. You are correct that nonalcoholic fatty liver disease will remain as the other major risk factor for this tumor.

**Ms McCurdy:** At our institution, we have just begun to use sofosbuvir. In academic, community, and government centers, it may take a long time to significantly reduce the incidence of HCV-related HCC with antivirals. We have enormous numbers of patients still untreated.

**Screening and Surveillance**

**Dr Marrero:** Patients with HCC develop the tumor in the presence of cirrhosis or chronic liver disease. It is not clear whether identifying patients with cirrhosis early enough—whether it is from fatty liver, hepatitis B, hepatitis C, autoimmune hepatitis, or other liver diseases—will reduce mortality. The only level 1 evidence we have is from a study of hepatitis B carriers in China.\(^8\) More than 18,000 people with HBV infection or a history of chronic hepatitis were randomized to a screening or control group. Screening included testing serum alpha-fetoprotein (AFP) and ultrasonography every 6 months. The data demonstrated that biannual screening reduced mortality from HCC by 37%.\(^8\) This study represents the only randomized trial showing that screening reduces mortality in the setting of HCC. In Western patients and those with hepatitis C, we do not have a randomized trial. Cohort studies suggest that surveillance may reduce mortality rates and improve outcomes, but they are not randomized.\(^9\) Current guidelines from the American Association for the Study of Liver Diseases,\(^10\) the National Comprehensive Cancer Network,\(^11\) the European Association for the Study of the Liver (EASL)/European Organisation for Research and Treatment of Cancer (EORTC),\(^12\) and the Asian Pacific Association for the Study of the Liver\(^13\) recommend surveillance with at least ultrasonography. The majority recommends both ultrasonography and AFP testing, but EASL/EORTC recommends ultrasonography alone.\(^13\) No data exist to show that surveillance with magnetic resonance imaging or computed tomography improves outcomes.

**Dr Abou-Alfa:** Short of the data from China, I agree that we do not know the optimal surveillance strategy. A valuable aspect of the Chinese study is that the end point was survival.\(^8\) Other studies have used surrogates for survival, leading to difficulty when interpreting the results.\(^14\) Because the screening is relatively noninvasive (blood work and ultrasonography), the risk–benefit ratio is low. Thus, ultrasonography and AFP testing should remain as acceptable screening tests.
Dr Marrero: I agree. AFP testing and ultrasonography may be controversial, but they are the best screening methods available.

Staging Systems

Dr Marrero: HCC staging is another controversial topic. Numerous staging and prognostic scoring systems have been used, including tumor-node-metastasis staging,15 the Okuda system,16 the Cancer of the Liver Italian Program (CLIP) score,17 the Barcelona Clinic Liver Cancer (BCLC) classification,18 the French Groupe d’Étude et de Traitement du Carcinome Hépatocellulaire prognostic classification,19 and the Chinese University Prognostic Index (CUPI).20 Although none of these is universally accepted, common variables among the systems include the use of tumor stage (eg, number of nodules, tumor size, presence of portal venous thrombosis) and hepatic function (eg, Child-Pugh class, presence of ascites, bilirubin level) to calculate prognosis.21 In addition, AFP level and patient performance status are used by some of the systems.

In my opinion, the BCLC system is the simplest and most evidence-based across multiple tumor stages (Table 122). It has been validated in Asia, Europe, and the United States, and it provides the best prognosis in terms of median survival.23 I disagree with the treatment strategy it recommends,18 but that is not the strength of the BCLC. However, for patients with advanced-stage HCC (stage C on the BCLC), the BCLC loses its prognosis value. Indeed, Huitzil-Melendez et al24 published a study showing that the BCLC was not the best system to use within specific risk strata.

Dr Abou-Alfa: BCLC performs well for early-stage disease, but it is not appropriate for late-stage disease. I agree with Dr Marrero that BCLC lags behind the actual science of the disease by putting patients into categories evolving in different directions. For example, in the category of advanced disease, patients are lumped into 1 group without any of the fine-tuning that other scoring systems provide, specifically CLIP17 and CUPI,20 both of which perform better than BCLC in the advanced setting.24

The BCLC also does not address etiology. What happens in patients with HBV-related HCC compared with HCV-related HCC? Do these patients perform the same? A good prognosis in the CUPI system does not imply a good prognosis in the CLIP system. We all aspire for an agreed-upon staging system that will make everybody happy. However, because the knowledge and treatment of HCC is so rapidly evolving, I do not think we will come to a consensus in the near future. HCC is more complex than previously thought.

On a practical level, if you are taking care of a patient with HCC, it is critical to recognize that liver cancer has 2 components, the tumor itself and liver dysfunction. Thus, it is important to have some measure of liver functionality, such as the Child-Pugh score (Table 225), as well as one of the tumor staging systems. The severity of underlying cirrhosis has a profound effect on all treatment decisions and can limit treatment modalities.

Dr Maluccio: I agree and I would like to offer a few thoughts from a transplantation perspective. At our institution, we try to determine as soon as possible whether liver transplantation is a reasonable expectation with respect to underlying liver disease, tumor-specific variables, and comorbid conditions that contribute to patient eligibility. For patients with underlying liver disease, we believe that liver transplantation provides the best long-term survival in early-stage HCC. We use the new United Network for Organ Sharing criteria for the diagnosis and leveraging of patients for transplantation.26 In these cases, I do not believe

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**Table 1. — Barcelona Clinic Liver Cancer Staging System**

<table>
<thead>
<tr>
<th>Stage</th>
<th>ECOG PS</th>
<th>Tumor Features</th>
<th>Liver Function</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>0</td>
<td>Single &lt; 5 cm</td>
<td>No PH</td>
<td>Surgery, RFA</td>
</tr>
<tr>
<td>A2</td>
<td></td>
<td>Single &lt; 5 cm</td>
<td>PH, Normal bili</td>
<td>Surgery, RFA</td>
</tr>
<tr>
<td>A3</td>
<td></td>
<td>Single &lt; 5 cm</td>
<td>PH, Abnormal bili</td>
<td>RFA, Transplantation</td>
</tr>
<tr>
<td>A4</td>
<td></td>
<td>3 tumors &lt; 3 cm</td>
<td>Not applicable</td>
<td>Transplantation, TACE</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td>Large multinodular</td>
<td>CP A–B</td>
<td>TACE</td>
</tr>
<tr>
<td>C</td>
<td>1–2</td>
<td>Vascular invasion or metastases</td>
<td>CP A–B</td>
<td>Systemic treatment</td>
</tr>
<tr>
<td>D</td>
<td>3–4</td>
<td>Any</td>
<td>CP C</td>
<td>Supportive care</td>
</tr>
</tbody>
</table>

bili = total bilirubin, CP = Child-Pugh, PH = portal hypertension, ECOG PS = Eastern Cooperative Oncology Group performance status, RFA = radiofrequency ablation, TACE = transarterial chemoembolization.

Table 2. — Child-Pugh Liver Disease Scoring System

<table>
<thead>
<tr>
<th>Classification of Cirrhosis</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>&lt; 2.0</td>
<td>2.0–3.0</td>
<td>&gt; 3.0</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>&gt; 3.5</td>
<td>3.0–3.5</td>
<td>&lt; 3.0</td>
</tr>
<tr>
<td>Prothrombin time (prolonged INR)</td>
<td>&lt; 1.7</td>
<td>1.7–2.3</td>
<td>&gt; 2.3</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Easily controlled</td>
<td>Poorly controlled</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>None</td>
<td>Minimal</td>
<td>Advanced</td>
</tr>
</tbody>
</table>

Class Assignment

<table>
<thead>
<tr>
<th>Total Points</th>
<th>Class</th>
<th>Liver Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>5–6</td>
<td>A</td>
<td>Compensated</td>
</tr>
<tr>
<td>7–9</td>
<td>B</td>
<td>Decompensated</td>
</tr>
<tr>
<td>10–15</td>
<td>C</td>
<td>Decompensated</td>
</tr>
</tbody>
</table>

INR = international normalized ratio.


that ultrasonography is sensitive enough; therefore, we have shifted to cross-sectional imaging to detect 1- to 2-cm lesions.

HCC staging systems incorporate multiple tumor-, liver-, and patient-specific factors. It is difficult to define which of those variables has the most prognostic value and which of the associated treatments has the best outcomes. With the new Patient Protection and Affordable Care Act requirements, health care professionals must justify more of what they do. For this reason, clinical research must focus on defining which treatments (eg, transplant, novel therapeutics) are best supported by the data.

Case Study in the Treatment of Early-Stage Hepatocellular Carcinoma

A 54-year-old man with chronic HCV infection failed antiviral therapy (interferon and ribavirin). Liver biopsy showed cirrhosis. Performance status was normal. Ultrasonography revealed a mass. Subsequent magnetic resonance imaging revealed an arterial enhancing mass $2.8 \times 2.7 \times 1.9$ cm in size with delayed hypointensity in the portal venous phase in the medial posterior right hepatic lobe adjacent to the inferior vena cava in segment 7. In addition, the portal vein was patent and no portal hypertension was present. An examination showed no ascites and no encephalopathy. The international normalized ratio (INR) was 1.0, bilirubin level was 1.1 mg/dL, albumin level was 3.9 g/dL, platelet count was 212,000/mm$^3$, creatinine level was 0.8 mg/dL, and AFP level was 9.4 ng/mL.

Dr Marrero: This case presents a patient with early-stage HCC. The potentially curative interventions for such patients include resection, ablative techniques (eg, radiofrequency ablation [RFA]), and liver transplantation.$^{10,11}$ Resection is the best choice when neither cirrhosis nor clinically significant portal hypertension is present. Six months following the resection, I would treat the HCV infection with newer antivirals, which may reduce the likelihood of recurrence.

The candidates for resection and transplantation are different. Patients amenable to resection can have chronic liver disease like hepatitis B or hepatitis C but do not have clinically significant portal hypertension, have a platelet count below 100,000/mm$^3$, are Child-Pugh class A, and have smaller tumors. The best data on resection come from a trial of patients with HCV infection led by Ikai et al.$^{27}$ Of more than 12,000 patients, the data demonstrated that the 5-year survival rates were approximately 70% in those with small tumors (3–5 cm) and no portal hypertension. These patients make up about 5% of all patients with HCC. Therefore, resection has a role in treatment, although it is relatively uncommon. RFA is another treatment option for patients with early-stage HCC but who are not candidates for resection. This option is limited to treating tumors up to 5 cm, but RFA can lead to excellent outcomes; the 5-year survival rate is close to resection.$^{28}$

Transplantations are indicated for a different patient population than candidates for resection. These are patients with portal hypertension, cirrhosis, and related complications, with either a single lesion of 2 to 5 cm, or 3 lesions less than 3 cm, and can be Child-Pugh class A, B, or C depending on the degree of portal hypertension or liver dysfunction. Transplantation is challenging because the procedure is limited by the availability of organ donors. The more than 30,000 new cases of HCC per year is far higher than the number of transplantations performed in the United States, which was approximately 5,900 in 2013.$^{29}$ In addition, out of those 5,900 patients, approximately 1,400 transplantations were performed for those with HCC.$^{30}$ Therefore, transplantation is a minor treatment for HCC due to the donor shortage—a shortage that has not been significantly ameliorated by the advent of living donor transplantation (currently < 5% of all transplantations).$^{30}$ The United Network for Organ Sharing criteria may also change to assign priority to
transplantation candidates without HCC. As a result, additional locoregional therapies for patients with early-stage disease may become available.

One of the challenges with resection, RFA, and other locoregional therapies is the high degree of recurrence, which is up to 80% to 90% by 5 years. Thus far, no adjuvant therapies significantly prevent recurrence. A few small trials have examined the use of interferon, but the results were inconclusive. The Sorafenib As Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma trial was a randomized phase 3 study that studied 1,100 patients who were given sorafenib or placebo following curative resection or RFA. However, preliminary data released in March 2014 showed that the primary end point of improved recurrence-free survival was not met.

Dr Maluccio: I agree that the proportion of patients with HCC currently transplanted in the United States has risen; it used to be that about 25% of transplantation candidates had HCC, but now that number is 30% to 35%. At the same time, the new organ allocation processes have made it difficult for these patients to receive transplantation in a timely manner, so the wait list is likely to drop off due to tumor progression. This makes the use of locoregional therapies such as RFA, chemoembolization, and radiotherapy to downstage the tumor and bridge the patient to transplantation that much more important. Unless we find a way to decrease the risk of recurrence following locoregional therapy, transplantation will still have the most impact.

I disagree with you on the outcomes of patients with HCV infection and early-stage disease; if you select patients within the established criteria, then the outcomes are identical for patients with cancer compared with patients without cancer. No survival disadvantage exists for choosing transplantation.

Dr Marrero: Transplantation may be the best available treatment, but the criteria for resection are different from the criteria for transplantation. The key is portal hypertension. Several studies show that patients without portal hypertension do well with surgery.

Dr Maluccio: Much depends on the general patient population. In patients with chronic HCV infection, the likelihood of having someone with well-preserved liver function, stages 2 to 3 fibrosis, and no portal hypertension is low compared with the total population. In my experience, the largest group of patients includes the middle-of-the-road CLIP 2 and Child-Pugh class B patients. These patients are often eligible for some form of liver-directed therapy. Concurrently, we must balance the positive impact of treatment on the tumor with the potential to worsen background liver function in this vulnerable patient subgroup.

This brings us back to defining up-front eligibility for transplantation as a means of establishing the goals of care across the treatment continuum. More enthusiasm exists in Asia with regard to the use of functional imaging to predict functional reserve prior to resection or liver-directed therapy. Some centers have adopted hepatobiliary scanning with 99mTc-mebrofenin. The theoretical advantage to this approach is that it would allow us to better stratify patients at risk for postoperative liver insufficiency and broaden the number of patients eligible for treatment with curative intent. Functional imaging is becoming more popular in patients with secondary liver tumors being considered for extended hepatectomies, in patients who have been heavily treated with chemotherapy, and in patients with moderate levels of steatosis. Volumetrics has been used as an indirect measure of liver reserve and has been used in the context of portal venous embolization prior to extended resections. However, volumetrics is less relevant in patients with underlying liver disease and HCC, because volumetrics does not provide information on the quality of the liver substance. Organ allocation is becoming increasingly more complex and resection will most likely be considered in patients with more vulnerable liver reserve. For this reason, I think that the integration of functional mapping into clinical practice is inevitable.

Another treatment option for patients unsuitable for standard locoregional therapies is stereotactic body radiotherapy (SBRT), a therapy included in the latest edition of the National Comprehensive Cancer Network guidelines as a potential treatment for this patient population. Just as with targeted radiation for early-stage lung cancer, SBRT may become an increasingly viable noninvasive option. The target patient population will overlap with those considered for resection or RFA, with the benefit of SBRT being noninvasive. SBRT has also been used as a bridge to liver transplantation and can be safely combined with locoregional therapies such as transarterial chemoembolization (TACE).

Dr Marrero: SBRT has potential for small tumors. Although the trials thus far have been small, I think SBRT has the potential to be superior to RFA. However, long-term data are immature at the moment, especially when compared with RFA, which has been around for decades. It will take time for us to understand late recurrences.

Case Study in the Treatment of Intermediate-Stage Hepatocellular Carcinoma

A 55-year-old man presents with chronic HCV cirrhosis. He has grade 1 esophageal varices (EV) and diabetes. He also complains of abdominal pain. The
A liver lesion is found 7 × 6.2 × 6.6 cm in size that is arterially enhancing, with delayed phase washout in the medial segment left lobe and an enhancing rim. The INR was 1.1, bilirubin level was 1.4 mg/dL, albumin level was 3.6 g/dL, platelet count was 65,000/mm³, creatinine level was 1.0 mg/dL, and AFP level was 45.6 ng/mL.

**Dr Marrero:** This is a patient with intermediate-stage, nonresectable, and nontransplantable disease. Therefore, the best option is transarterial chemoembolization. At about 6 weeks following treatment, I would evaluate the response and repeat chemoembolization if residual disease is present.

For patients with an open main portal vein, major treatment options include intra-arterial therapies such as TACE or transarterial embolization (TAE). These techniques have been well studied and are a mainstay of treatment for these patients; however, evidence of a survival benefit is mixed. Intra-arterial embolization with or without chemotherapy has modest efficacy and a high recurrence rate. Two methods have been tested to improve the technique: (1) the use of drug-eluting beads, which phase 1 and 2 trials have shown leads to small improvements in efficacy and safety over conventional TACE, and (2) radioembolization with yttrium-90 microspheres (Y-90). The optimal use of Y-90 is unclear, and each center uses Y-90 differently.

**Dr Abou-Alfa:** The confusion comes from a lack of data. Notwithstanding 2 older studies that compared TACE and supportive care, no comparative trials exist to advise us on what to do. A randomized phase 2 study that compared TACE with TAE (ie, chemoembolization vs embolization) showed no difference in outcomes. In addition, patients with metastatic disease receiving embolization alone do worse than those receiving systemic therapy. Therefore, this treatment requires further clarification. Salem et al use Y-90 therapy in the setting of portal venous thrombosis whenever embolization is not applicable. However, there are no randomized data in that setting.

**Dr Maluccio:** One frustrating challenge to HCC treatment is the variable approach to liver-directed therapies. Dr Abou-Alfa and I agree on the lack of data concerning the comparative use of TAE, chemoembolization, and Y-90. In addition, with the Patient Protection and Affordable Care Act, the cost associated with different treatment options will become a major factor in future treatment decisions.

**Case Study in the Treatment of Advanced-Stage Hepatocellular Carcinoma**

A 59-year-old woman has well compensated alcoholic cirrhosis. She has grade I EV, hypertension, and no encephalopathy. She reported that she has not consumed alcohol in 3 years. She also stated that she has lost 5 pounds in the last 2 months. She has never been treated with antiviral therapy. Computed tomography revealed a 9-cm infiltrating tumor in the left lobe of the liver with portal vein tumor thrombus in the left and main portal vein. On examination, she has no ascites but has mild abdominal pain. The INR was 1.2, bilirubin level was 1.7 mg/dL, albumin level was 3.5 g/dL, platelet count was 112,000/mm³, creatinine level was 0.8 mg/dL, and AFP level was 32,992 ng/mL.

**Dr Marrero:** This patient has advanced-stage HCC and should be treated with twice-daily sorafenib 400 mg. Close follow-up is needed to proactively manage any possible adverse events. In addition, this patient must be educated about ways to avoid palmar-planter erythrodysesthesia (hand-foot syndrome) and possible diarrhea.

In patients with advanced-stage HCC, treatment with the antiangiogenic multikinase inhibitor sorafenib is the standard of care. Two phase 3 studies showed that sorafenib modestly improved survival in these patients (mostly Child-Pugh class A), findings that led to the FDA approval of sorafenib in 2007 (Fig 2). Sorafenib remains the only systemic therapy shown to improve overall survival in unresectable HCC across multiple patient populations. A prospective, noninterventional study of more than 3,000 patients with unresectable HCC treated with sorafenib showed that the adverse-event profile of sorafenib was fairly similar between Child-Pugh class A and B patients. The Child-Pugh class A cohort fared better than the Child-Pugh class B in terms of overall survival, probably due to the difference in liver function. Nonetheless, it is still difficult to determine which patients will do well when treated with sorafenib. No good data exist to make a definitive conclusion.

**Dr Abou-Alfa:** The lack of randomized data for Child-Pugh class B patients is a challenge. In a subgroup analysis of a phase 2 study, myself and coauthors showed that patients with Child-Pugh class B performed worse with regard to liver performance, including increased bilirubin, worsening ascites, and worsening encephalopathy, even though the pharmacokinetic profile was similar among patients with Child-Pugh classes A and B. In a phase 1 trial, Miller et al evaluated patients with advanced liver dysfunction. The study concluded that patients assigned to the HCC cohort who had a total level of bilirubin between 1.5 and 3 mg/dL should take a one-half dose of sorafenib.
(400 mg daily), patients with a bilirubin level above 3 mg/dL should not be recommended a dose, and patients with an albumin level below 2.8 mg/dL should take 1 pill a day (200 mg daily).

**Dr Marrero:** If the common adverse events seen in patients taking sorafenib are hand-foot syndrome and diarrhea, how can we prevent or treat these effects?

**Ms McCurdy:** We are trying to provide education and support so that patients do not give up their medication and present to a health care professional after having discontinued their medication 2 weeks before. Therefore, it is important to closely monitor patients with phone calls and clinic visits.

With regard to diarrhea, I discuss with a patient about what he or she can expect and how to self-treat with over-the-counter loperamide and dietary changes, including the removal of caffeine from the diet. At my center, we are trying to prevent the patient from waiting 2 weeks to call, perhaps after having been to the emergency department because he or she is dehydrated. With regard to hand-foot syndrome, we show patients pictures early on so they understand what to expect. We also educate patients on emollient lotions and early treatment options, including the use of products like petrolatum-based ointments, salicylic acid, or urea-based creams if they develop calluses.

Patient adherence to oral therapies is difficult. There is nothing as disappointing as starting a patient on therapy and then having him or her discontinue treatment after 1 week. Selecting patients committed to treatment and ready to tackle any adverse events is important for maximizing adherence to treatment.

**Dr Marrero:** In addition to sorafenib, other novel agents are in development for the treatment of patients with advanced disease (Table 3). Several cancer mesenchymal epithelial transcription factor (c-MET) inhibitors, multikinase inhibitors, antiangiogenic agents, and transforming growth factor beta 1 inhibitors are advancing into late-phase trials. The mechanisms of action of selected targeted therapies for patients with advanced HCC are shown in Fig 3.

**Dr Abou-Alfa:** A tyrosine kinase receptor for the hepatocyte growth factor, c-MET is a new target for novel therapeutics. For example, cabozantinib, which is an inhibitor of MET and vascular endothelial growth
factor receptor 2, has shown promising efficacy in a cohort of 41 patients with advanced HCC.\textsuperscript{64} In 78% of patients, tumor regression was observed per the Response Evaluation Criteria In Solid Tumors rules, a 5% confirmed partial response rate was seen, and the median progression-free survival rate for the cohort was estimated to be 4.2 months.\textsuperscript{64} The most common grade 3/4 adverse events were diarrhea (17%), palmar-plantar erythrodysesthesia (15%), and thrombocytopenia (10%). A pivotal phase 3 study of cabozantinib is underway (NCT01908426).

Tivantinib, a selective oral inhibitor of MET, has been studied in a phase 2, double-blind, randomized trial of patients with advanced HCC and Child-Pugh class A cirrhosis who had progressed on or were unable to tolerate first-line systemic therapy.\textsuperscript{61} For patients with MET-high tumors, the median time to progression was longer with tivantinib than for those assigned to placebo (2.7 vs 1.4 months). The most common grade 3 or worse adverse events in the tivantinib group were neutropenia and anemia.\textsuperscript{61} A pivotal phase 3 trial is underway (NCT01755767), and other phase trials of the MET inhibitors onartuzumab (NCT01897038), pegylated arginine deiminase (NCT01287585), and ramucirumab (NCT01140347) are ongoing.

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Table 3. — Overview of Multidisciplinary Treatment Options for HCC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Suggested Indications*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potentially Curative Therapies</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Surgical resection | CP class A  
No portal hypertension  
Solitary mass without major vascular invasion  
Adequate liver reserve  
Suitable liver remnant |
| Liver transplantation (CLT or LDLT) | CP class A  
PS 0  
Meets UNOS criteria (tumor ≤ 5 cm in diameter or 2–3 tumors ≤ 3 cm each, no macrovascular involvement, no extrahepatic disease) |
| **Locoregional Therapies** | |
| Ablation (radiofrequency, cryoablation, PEI, microwave) | Nontransplantation candidates  
Tumors in accessible location  
May be curative in tumors ≤ 3 cm |
| Arterially directed therapies (TAE, TACE, DEB TACE, radioembolization) | CP class A, B  
Nontransplantation candidates  
Unresectable tumors 3–5 cm irrespective of location  
Bilirubin ≤ 3 mg/dL  
No main portal venous thrombosis |
| 3-dimensional conformal radiotherapy | Patients unfit for surgery, transplantation, RFA, embolization, or chemotherapy |
| Stereotactic radiotherapy | CP class A or B  
Nontransplantation candidates  
1–3 unresectable tumors with a cumulative diameter < 6 cm  
No extrahepatic disease |
| **Systemic Therapies** | |
| Sorafenib | CP class A or B  
Advanced-stage or metastatic HCC  
Nontransplantation candidates  
Unresectable lesions > 5 cm  
Normal bilirubin |
| Cytotoxic chemotherapy | Nontransplantation candidates  
Unresectable lesions  
Adequate hepatic function  
Administered in clinical trials only |

*Continues on page 13
Other novel approaches include the multikinase inhibitor regorafenib and the transforming growth factor beta 1 receptor I kinase inhibitor LY2157299. Antitumor activity was observed in a phase 2 trial of regorafenib in sorafenib-refractory patients with BCLC stage B or stage C HCC status with Child-Pugh class A liver function. Disease control was achieved in 26 of the 36 patients, median time to progression was 4.3 months, and the median overall survival rate was 13.8 months. A phase 3 trial evaluating regorafenib in sorafenib-refractory patients with HCC has begun enrollment (NCT01774344).

LY2157299 has also been tested in a phase 2 trial of patients with advanced HCC who progressed on sorafenib or who were ineligible to receive sorafenib (NCT01246986). The median time to progression was 12 weeks in the overall population and 18.3 weeks in patients naive to sorafenib. Based on the latest interim analysis, the median overall survival rate was 36 weeks. In patients who responded to AFP, the median overall survival rate was 93.1 weeks compared with 29.6 weeks in those who did not respond to AFP. The most common grade 3/4–related adverse events were neutropenia, fatigue, and anemia.

Combining sorafenib with chemotherapy is another promising direction in treatment. One key study is examining sorafenib plus doxorubicin compared with sorafenib alone. The primary end point is overall survival. Following the first planned interim analysis, the trial continued patient accrual, so

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### Table 3. — Overview of Multidisciplinary Treatment Options for HCC (continued)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Suggested Indicationsa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Novel Agents in Clinical Trials</strong></td>
<td></td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>CP class A (NCT01908426)</td>
</tr>
<tr>
<td></td>
<td>PS 0 or 1</td>
</tr>
<tr>
<td></td>
<td>Noncurative treatment candidates</td>
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<tr>
<td></td>
<td>Prior sorafenib</td>
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<tr>
<td>Tivantinib</td>
<td>CP class A (NCT01755767)</td>
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<td></td>
<td>PS 0 or 1</td>
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<tr>
<td></td>
<td>Inoperable HCC</td>
</tr>
<tr>
<td></td>
<td>Not eligible for or completed local therapy</td>
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<tr>
<td></td>
<td>High c-MET expression</td>
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<tr>
<td></td>
<td>Prior sorafenib</td>
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<tr>
<td>Onartuzumab</td>
<td>CP class A (NCT01897038)</td>
</tr>
<tr>
<td></td>
<td>PS 0 or 1</td>
</tr>
<tr>
<td></td>
<td>Advanced-stage or metastatic HCC</td>
</tr>
<tr>
<td>ADI-PEG 20</td>
<td>CP class B7</td>
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<tr>
<td></td>
<td>Progressive disease after systemic agent</td>
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<tr>
<td></td>
<td>Adequate hepatic and renal function (NCT01287585)</td>
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<tr>
<td>Ramucirumab</td>
<td>CP class A (NCT01140347)</td>
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<tr>
<td></td>
<td>PS 0 or 1</td>
</tr>
<tr>
<td></td>
<td>BCLC-C or BCLC-B not amenable to locoregional therapy</td>
</tr>
<tr>
<td></td>
<td>Prior sorafenib</td>
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<tr>
<td></td>
<td>Liver mass ≥ 2 cm</td>
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<tr>
<td>Regorafenib</td>
<td>CP class A (NCT01774344)</td>
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<td></td>
<td>PS 0 or 1</td>
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<td></td>
<td>BCLC-B or BCLC-C</td>
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<td>Failed prior sorafenib</td>
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<td>LY2157299</td>
<td>CP class A or B7</td>
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<td></td>
<td>PS 0 or 1 (NCT01246986)</td>
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<td></td>
<td>Noncurative surgery candidates</td>
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<tr>
<td></td>
<td>Failed prior sorafenib</td>
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</table>

aNot all indications and contraindications listed; refer to references 10 and 11 for a complete description.

BCLC = Barcelona Clinic Liver Cancer, CLT = cadaveric liver transplantation, CP = Child-Pugh, DEB = drug-eluting beads, HCC = hepatocellular carcinoma, LDLT = living donor liver transplantation, PEI = percutaneous ethanol injection, PS = performance status, RFA = radiofrequency ablation, TACE = transcatheter arterial chemoembolization, TAE = transarterial bland embolization, UNOS = United Network for Organ Sharing. Data from references 10 and 11.
we have to stay tuned to see what happens. Other ongoing studies are examining the use of doxorubicin plus sorafenib following sorafenib failure and the efficacy of a modified leucovorin (folinic acid), fluorouracil, and oxaliplatin regimen plus sorafenib.

It is also worth mentioning many negative results from HCC trials have been seen in recent years. Trials of bevacizumab, brivanib, sunitinib, linsitinib, and everolimus did not meet their end points. Various regimens have not fared much better; for example, results from the sorafenib plus erlotinib and bevacizumab plus erlotinib trials were disappointing. Nonetheless, the number of novel targeted agents in late-stage trials is encouraging, and we are hopeful for new FDA approvals in the future.

**Conclusions**

**Dr Marrero:** Treating hepatocellular carcinoma and underlying liver disease necessitates a multimodal approach that may combine surgical resection, liver transplantation, locoregional therapies, molecular-targeted therapy, and the management of adverse events. Therefore, patients with hepatocellular carcinoma should receive optimal care managed by a multidisciplinary team consisting of several specialists. An integrated approach that involves ongoing face-to-face discussion between hepatobiliary and transplantation surgeons, hepatologists, interventional radiologists, gastroenterologists, pathologists, oncologists, primary care physicians, and nurses will ensure the development of an individualized care plan to best fit the needs of each patient, expedite treatment, and improve outcomes.
Key Takeaways

• The burden of hepatocellular carcinoma (HCC) is increasing. It is now the second most common cause of cancer-related mortality worldwide and is increasing by approximately 3% per year in the United States.

• Regular surveillance with ultrasonography combined with alpha-fetoprotein testing for patients at risk is recommended in order to diagnose HCC at an earlier stage and improve survival.

• Each of the staging and prognostic scoring systems guiding HCC treatment have advantages and disadvantages, although the common variables include the use of tumor burden, tumor size, measures of liver function, and performance status to calculate prognosis.

• Liver transplantation and resection are the only potentially curative treatments for HCC, although a minority of patients is eligible for these treatment options.

• Locoregional therapies, including ablation, arterially directed therapies, and radiotherapy, are a mainstay of treatment for intermediate-stage HCC, although the evidence for a survival benefit is modest.

• The multikinase inhibitor sorafenib remains the only approved systemic therapy for patients with unresectable HCC.

• Despite recent setbacks, many novel agents for advanced-stage/metastatic HCC are advancing into late-stage trials, including cancer mesenchymal epithelial transcription factor inhibitors, multikinase inhibitors, antiangiogenic agents, and transforming growth factor beta 1 inhibitors.

• Optimal management of HCC should involve careful coordination of multiple specialists, including surgeons, hepatologists, radiologists, gastroenterologists, pathologists, and oncologists.

References


