

Recent Progress in Understanding, Diagnosing, and Treating Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is one of the few cancers in which a continued increase in incidence has been observed over several years. As such, there has been a focus on safe and accurate diagnosis and the development of treatment algorithms that take into consideration the unique complexities of this patient population. In the past decade, there have been improvements in nonsurgical treatment platforms and better standardization with respect to the diagnosis and patient eligibility for liver transplant. How to navigate patients through the challenges of treatment is difficult and depends on several factors: 1) patient-related variables such as comorbid conditions that influence treatment eligibility; 2) liver-related variables such as Child-Pugh score; and 3) tumor-related variables such as size, number, pattern of spread within the liver, and vascular involvement. The objectives of this review are to put into perspective the current treatment options for patients with HCC, the unique advantages and disadvantages of each treatment approach, and the evidence that supports the introduction of sorafenib into the multidisciplinary management of HCC. *CA Cancer J Clin* 2012;62:394-399. © 2012 American Cancer Society.

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Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related deaths worldwide, with the incidence on the rise both in the United States and abroad.^{1,2} Globally, there are approximately 750,000 new cases of liver cancer reported per year. Population-based studies show that the incidence rate continues to approximate the death rate, indicating that most of the patients who develop HCC die of it.¹ Five-year survival rates in the United States have improved modestly to approximately 26%, an improvement that is believed to be associated with improved surveillance in identifiable high-risk patients (ie, those with hepatitis B and C viruses) and surgical intervention (resection or transplant) for patients with early-stage disease.³ The vast majority of HCC occurs in the setting of chronic liver disease from viral hepatitis, alcohol abuse, and/or nonalcoholic steatohepatitis (NASH). The prevention of HCC must therefore focus on the prevention of hepatitis B and C virus transmission and the institution of guidelines to reduce the prevalence of obesity.^{4,5}

Consensus guidelines have been published by several organizations, including the American Association for the Study of Liver Disease (AASLD), National Comprehensive Cancer Network (NCCN), and European Association for the Study of the Liver (EASL) to standardize the approach to diagnosis and treatment.⁶⁻⁸ As is true with most disease processes, HCC is more effectively treated when it is diagnosed at an early stage. The best chance for early diagnosis comes from the surveillance of patients known to be at high risk. This includes patients with cirrhosis from any cause and carriers of hepatitis B.⁷ The 2012 NCCN guidelines recommend screening high-risk patients with serum α -fetoprotein (AFP) and liver ultrasound every 6 months to 12 months. A rising AFP associated with a liver nodule measuring larger than 1 cm raises suspicion for HCC and warrants evaluation with cross-sectional imaging.⁷

Criteria for the diagnosis of HCC have evolved over the past decade. To minimize the use of percutaneous biopsy and its inherent risks in patients with underlying liver disease (tract seeding, bleeding, etc), the AASLD, NCCN, and EASL working groups have adopted imaging criteria that predict cancer with an acceptable accuracy.^{6,8} On contrast-enhanced images using computed tomography (CT) or magnetic resonance imaging (MRI), the imaging characteristics of HCC are early arterial enhancement and venous phase washout, which are related to the fact that these are hypervascular lesions supplied predominantly by branches of the hepatic artery. In the setting of chronic liver disease, lesions measuring larger than 1 cm that demonstrate these imaging characteristics on triple-phase CT or contrast-enhanced MRI are classified as HCC. This is a change from previous guidelines, where lesions measuring between 1 cm and 2 cm required characteristic

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enhancement on both imaging modalities (CT and MRI) to define HCC. Despite changes in the imaging criteria, only lesions measuring greater than 2 cm with characteristic enhancement are eligible for Model for End-Stage Liver Disease (MELD) exception points for liver transplant. Some centers have adopted MRI with novel contrast agents like gadoxetic acid, to better define lesions that do not meet criteria on conventional arterial and venous phase imaging alone. Lesions suspicious for HCC appear darker than background liver on T1-weighted (hepatocyte phase) imaging.⁹ To date, gadoxetic acid-enhanced MR imaging has not changed the diagnostic paradigm that is currently used to determine treatment eligibility despite reports of improved imaging specificity.¹⁰

Several clinical staging systems, including the Cancer of the Liver Italian Program (CLIP)¹¹ and the Barcelona Clinic Liver Cancer (BCLC),¹² have emerged to help predict prognosis and stratify patients for treatment. The goal of each is the same: to better define the prognostic weight of clinical variables on outcome in patients with HCC who are being considered for treatment or clinical trials. The CLIP system includes the Child-Pugh score, tumor morphology (uninodular, multinodular, or extensive), AFP, and the presence or absence of portal vein thrombosis.¹¹ The BCLC system includes the Child-Pugh score, clinical performance status, and tumor stage (solitary, multinodular, vascular invasion, or extrahepatic spread) and categorizes patients into early HCC (BCLC stage A1-A4), which includes well-compensated (Child-Pugh class A) liver reserve with an excellent performance status and limited tumor burden. Intermediate HCC (BCLC stage B) includes moderate liver reserve (Child-Pugh class A and B), excellent performance status, and multinodular tumors. Advanced HCC (BCLC stage C) includes moderate liver reserve (Child-Pugh class A and B), vascular invasion or extrahepatic spread, and a vulnerable performance status (Eastern Cooperative Oncology Group [ECOG] 1-2). The difference in estimated survival at 3 years in patients with untreated BCLC stage A disease versus those with BCLC stage C disease is 50% versus 8%, respectively.¹² The impact of any given treatment on patients with more advanced disease is unclear. Modifications of these staging systems with the addition of plasma-based tumor markers such as vascular endothelial growth factor¹³ or insulin-like growth factor-1¹⁴ have been proposed to improve the prognostic stratification of patients with advanced HCC and better select which of these patients are appropriate for treatment.

Liver Transplant

Liver transplant is considered the most effective method to treat both the cancer and the underlying liver disease from which most cases of HCC develop. Transplant eligibility is based on the size and number of tumors, and criteria have

been established to optimize cancer-specific outcomes. The most commonly used criteria worldwide are the Milan criteria,¹⁵ in which patients with up to 3 foci of HCC measuring less than 3 cm or one tumor measuring less than 5 cm are eligible for liver transplantation. These patients experienced a 5-year overall survival rate (75%) that paralleled the survival rate observed in patients undergoing transplant without cancer at that time.¹⁵ Other centers, such as the University of California at San Francisco (UCSF), have broadened their criteria (one tumor measuring less than 6.5 cm or 2 to 3 tumors, none of which measures greater than 4.5 cm, with the total tumor diameter not to exceed 8 cm) for eligibility based on outcome-based evidence that less strict parameters do not adversely affect overall survival.^{16,17} With improvements in liver-directed therapies for HCC, downstaging of patients into either Milan or UCSF criteria has emerged as a reasonable approach with which to select patients.¹⁸ What has become apparent is that progression of disease despite liver-directed therapies identifies those cancers that are at a high risk for recurrence after transplant. Demonstration of a response to liver-directed therapies prior to transplant in combination with surveillance over a period of time before committing to transplant allows centers to select out individuals with more favorable biology and broaden patient eligibility without compromising cancer-specific survival.

Surgical Resection

Liver resection remains the gold standard for patients with resectable HCC that develops in the setting of normal liver substance. However, most patients with HCC have diseased liver parenchyma and resection in this population is more fraught, with the potential for complications. For this reason, preservation of the liver parenchyma is critical, and treatment requires a balance between the effect of any surgical intervention short of transplant and the potentially detrimental effect of this treatment on a vulnerable and “high-risk” remnant. Most published resection series focus on patients with single tumors or limited disease burden up to a certain size and well-preserved (Child-Pugh class A) function. As liver-directed therapies have improved, the gap in overall survival between liver-directed therapies and resection in patients with underlying liver disease has narrowed substantially.¹⁹ This is due in part to the high rate of recurrence or de novo tumor emergence in the liver remnant. The recurrence rate after resection is approximately 50% at 2 years and 75% at 5 years in most series.²⁰

In regions of the world where hepatitis B is the dominant risk factor for cancer, resection is used more commonly for several reasons, including: 1) cadaveric organ availability is limited; 2) centers outside the United States rely more on living related donor pools in which the human investment in the process is greater; and 3) a higher percentage of

patients with hepatitis B have preserved liver function, making resection safer. Therefore, to minimize unnecessary risk to a living donor and to help select patients who would benefit the most from a liver transplant, resection is used as upfront treatment, with transplant reserved as a salvage option in the event that the cancer recurs or the liver function worsens over time.

The natural history of HCC in the background of NASH would suggest a higher percentage of patients with noncirrhotic livers and a lower rate of recurrence (or de novo tumor emergence) than in either hepatitis B or hepatitis C.²¹ For this reason, resection may emerge as a reasonable option in this patient population as well. Resection versus transplant in patients with NASH must be evaluated based on underlying liver reserve.

Embolization

Most patients are not candidates for resection or transplantation at the time of diagnosis because of either the extent or distribution of tumor, underlying liver function, or medical comorbidities. The dual blood supply to the liver has allowed hepatic artery-based therapies to develop over the past 30 years. Whereas non-tumor-bearing liver parenchyma receives its nutrient supply predominantly from the portal vein, most HCC are supplied for the most part by the hepatic artery. Catheter-based techniques take advantage of this unusual architecture to deliver intraarterial therapy directly to the tumor bed. Several different treatments have been administered by catheter via the artery to treat patients with HCC, including bland embolization, transarterial chemoembolization (TACE), chemoembolization with drug-eluting beads (DEBs), and radioembolization. To date, there have been no prospective or randomized trials defining any of the available options as superior in terms of survival. Centers around the world have therefore gravitated toward the technique that works best in their hands. Complications common to all catheter-based therapies for HCC include postembolization syndrome (fever, nausea, and pain), nontarget embolization (stomach, gallbladder, duodenum, and pancreas), and liver failure (less than 2% in well-selected patients).

Bland Particle Embolization

Bland particle embolization is based on the unique dependence of HCC on the hepatic artery. Small particles (40 μm -120 μm) are injected into the arterial supply to the tumor to cause terminal vessel blockade and result in ischemic necrosis of the tumor. The 5-year data on response and survival suggest cancer-specific outcomes that are comparable to those of other catheter-based techniques.²² The results of bland embolization are essentially immediate, with radiologic evidence of tumor necrosis noted within hours of the procedure. This is a particularly useful feature in patients who present

with significant tumor burden, in whom further progression may render them untreatable. Other theoretical advantages of bland embolization include: 1) the particles come in a range of sizes that can effectively address unique vascular characteristics of the tumor, including intrahepatic portal systemic shunting; 2) lower periprocedural cost; 3) no delay between the initial arteriogram and treatment delivery; 4) no chemotherapy-related or radiation-related side effects; 5) the ability to re-treat due to better preservation of intrahepatic arteries after treatment²³; and 6) fewer institutional infrastructure requirements, such as radiation safety.

Much of the debate about where bland particle embolization fits in the current treatment paradigm stems from a large prospective randomized trial comparing supportive care, bland embolization, and TACE.²⁴ This study was terminated after interim analysis showed a survival advantage of TACE over supportive care. At the time the study was closed, there was no significant difference in outcome noted between the 2 treatment arms (bland vs chemoembolization). The results for TACE, however, were on par with those published in a series of patients with HCC who were treated with bland embolization at the Memorial Sloan-Kettering Cancer Center.²² This same year, Camma et al published one of 2 meta-analyses comparing catheter-based treatment of HCC that did not reveal any benefit in survival with the addition of bolus intraarterial chemotherapy to bland embolization.²⁵ In 2006, the Society of Interventional Radiology published a consensus statement to this effect.²⁶

Chemoembolization-DEB

Doxorubicin-eluting beads (DEB) are another catheter-based, liver-directed therapy. The use of an eluting bead is considered to be an improvement on conventional chemoembolization (TACE), in which a hydrophilic chemotherapeutic agent(s) (with or without lipiodol) was injected into the liver via the hepatic artery. To prevent washout of the chemotherapy from the tumor bed and thereby allow prolonged contact between chemotherapeutic agent(s) and the tumor cells, the feeding artery was then occluded with particles or gelfoam. Conventional TACE largely has been replaced by embolization with DEBs. DEBs are preformed deformable microspheres that are loaded with doxorubicin (up to 150 mg per treatment). The pharmacokinetic profile of DEBs is significantly different from that noted with conventional TACE, with evidence that the peak drug concentration in the serum is an order of magnitude lower for DEBs compared with TACE. The objective response rate by EASL criteria has been reported as between 70% to 80%.²⁷ One-year and 3-year survival rates of 89.9% and 66.3%, respectively, have been reported in a heterogeneous cohort of patients with BCLC stage A to C disease.²⁸ The advantages of DEB overlap with those related to bland embolization: 1) the ability to treat multiple tumors in different regions of

the liver during the same procedure; 2) the use of superselective techniques that limit toxicity to normal liver substance; and 3) the ability to repeat the procedure several times over the lifetime of the patient.

Radioembolization

Yttrium-90 is a beta emitter that can be loaded into glass or resin microspheres and administered via a microcatheter into the hepatic artery. TheraSphere glass microspheres (Nordion, Ottawa, Ontario, Canada) are approved by the US Food and Drug Administration for the treatment of patients with HCC. The spheres are preferentially taken up by tumor vasculature and, as such, deliver a high dose of radiation directly to the tumor bed. The half-life of the bead allows for treatment to take place over weeks, with the theoretical advantage of an improvement in the durability of response.²⁹ Other advantages of yttrium-90 include: 1) better tolerability in patients with vulnerable liver reserve (Child-Pugh class B) when used in a selective manner; 2) because of the size and number of particles, there is little embolic effect; and 3) the effect of radiation is less acute than any of the embolic techniques, and there are fewer postembolization syndromes than commonly seen after TACE, DEBs, or bland particle embolization. Yttrium-90 is delivered in the outpatient setting. The objective response rate is comparable to that of other catheter-based modalities and depends on several factors including the size of the lesion, pattern of spread within the liver (unilobular vs bilobular), and vascularity of the lesion noted on planning arteriogram.³⁰ In patients with limited liver reserve (Child-Pugh class C), some centers will still consider treatment, but usually as a bridge to a timely transplant. There are disadvantages specific to radioembolization: 1) the need for a mapping procedure to embolize potential nontarget vasculature arising from or near the target vessels (ie, right gastric artery, falciform artery, or gastroduodenal artery); 2) the risk of shunting radioactive particles into the lung, resulting in pulmonary fibrosis; and 3) radiation-induced liver toxicity (approximately 1%-3%). Nontarget radioembolization compared with TACE or bland embolization to the lung or gastrointestinal tract can be particularly devastating.

Tumor evaluation after any catheter-based treatment is difficult. Instead of a decrease in the size and volume of tumor as seen after a response to chemotherapy, a change in enhancement from early arterial to no enhancement is widely accepted as a response. Therefore, the modified Response Evaluation Criteria In Solid Tumors criteria (mRECIST) have been established for this purpose. The mRECIST report the percentage of tumor that has imaging findings consistent with necrosis rather than absolute size measurements.³¹ After radioembolization, 1-month response rates are difficult to measure because there are often radiation-induced changes in the treated liver. In cases in which AFP is

elevated, changes in AFP may provide better insight into early response. Three months is a far better judge of maximal response to treatment. Continued response to yttrium-90 even after 3 months has also been observed.

Stereotactic Body Radiation Therapy

Stereotactic body radiation therapy (SBRT) is a type of targeted radiation therapy whereby computer modeling is used to delineate the treatment area. Using an immobilization device, respiratory variation is limited during treatment. SBRT is noninvasive, delivered in the outpatient setting, and very well tolerated. It has been studied in single lesions measuring up to 6 cm or in up to 3 tumors, none of which measured greater than 3 cm. There must be at least 700 cc of liver volume outside the treatment field.^{32,33} The phase 1 data escalated the dosage up to 16 grays in 3 fractions. For the patients with Child-Pugh class A disease, there was no dose-limiting toxicity noted. In patients with Child-Pugh class B disease, dose-limiting toxicities were encountered and the protocol was changed to a protracted 5-fraction course with the same total dose. This diminished the toxicity to levels noted in patients with Child-Pugh class A disease.³² The phase 2 data from the same cohort of patients showed a 2-year tumor control rate of 90%.^{34,35} In patients treated with larger tumors off protocol, the response rates are still greater than 90%, although the long-term tumor control rate is lower with increasing size (unpublished data).

Ablation

Ablation is a potentially curative treatment option for patients with early-stage disease. The success of ablation is highest with lesions measuring less than 2 cm to 3 cm and decreases significantly in tumors measuring larger than 3 cm.³⁶ For larger or paucifocal tumors, ablation may be performed in combination with embolization. In solitary tumors measuring up to 7 cm, this combination has shown to provide 5-year survival on par with surgical resection.³⁷

Both thermal ablation (radiofrequency ablation, microwave, laser-induced interstitial thermotherapy, high-intensity focused ultrasound, and cryoablation) and chemical ablation (ethanol and acetic acid) have been used to treat patients with HCC. HCC is the ideal target for ablation because in most cases it is a soft tumor surrounded by a fibrotic liver. This is the source of the so-called "oven effect," where heat applied to the tumor is insulated by the cirrhotic liver. The combination of soft tumor and hard liver is also beneficial in chemical ablation because the ethanol or acetic acid can diffuse easily in the soft tumor but is kept from escape by the cirrhotic liver.^{38,39}

Which ablative technique is appropriate depends on the location and size of the target tumor. For example, radiofrequency ablation is susceptible to the "heat sink" effect, in which large vessels close to the tumor can take the

heat away in flowing blood and prevent complete ablation. For a tumor close to a large vessel, microwave ablation may be a better choice because it is not as susceptible to this effect. The long-term efficacy for either technique drops substantially with increasing size and number of lesions.⁴⁰

Ablation is often performed under general anesthesia, but it may be performed percutaneously, laparoscopically, or at open surgery. Similar to catheter-based techniques, RECIST criteria are not useful in the evaluation of imaging response. After ablation, the ideal response is a necrotic, nonenhancing “lesion” measuring at least 2 cm larger than the treated tumor (including a 1-cm circumferential margin.) As a bridge to transplant, ablation can therefore complicate the evaluation process because the ablation zone is larger than the original tumor and transplant criteria are based on tumor size. In patients being considered for transplant, the patient should be listed with the appropriate tumor characteristics prior to treatment.

Chemotherapy

Sorafenib is approved by the US Food and Drug Administration for the treatment of HCC. Since its approval, there has been a surge in the number of patients with HCC being treated with the drug regardless of their tumor stage. The use of sorafenib is based on phase 2 and phase 3 data in patients with advanced metastatic HCC, with the treatment group showing close to a 3-month survival advantage over the nontreated group.⁴¹⁻⁴³ The objective response rate rests at around 2%, with most of the effect associated with the stable disease rate of 35% to 71% noted in the phase 2 and phase 3 trials, respectively. Over 80% of the patients in the phase 3 study had been previously treated with liver-directed therapies (chemoembolization) prior to entry. The response rate to liver-directed therapies remains above 70% and therefore sorafenib must be considered within the context of all treatment options currently available. Sorafenib has been used in combination with liver-directed therapies, with reasonable toxicity profiles and a slight improvement in efficacy noted.⁴⁴ Dose delays and/or reduction have been required in the vast majority of patients. Recent phase 3 data investigating the benefit of sorafenib in the adjuvant

setting after embolization are less convincing.⁴⁵ Short of a small series, sorafenib has not been studied in the neoadjuvant setting either before liver-directed therapy, resection, or transplant. Using lessons learned from other antiangiogenic compounds used in the neoadjuvant setting, this introduces potential periprocedural or perioperative complications that would compromise either the ability to deliver therapy successfully or patient/graft survival. For example, with catheter-based techniques, the arterial pruning associated with antiangiogenic agents may impact the delivery of the small micron particle into the tumor bed. In the context of liver transplant, there are several reasons to avoid sorafenib preoperatively: 1) transplant patients are often at a higher baseline risk of wound healing complications due to nutritional deficiencies; 2) arterial complications are devastating and often life-limiting after liver transplant; and 3) the near 70% stable disease rate observed in the phase 3 trials may mask the occult metastatic disease that would make transplant inappropriate. The combination of antiangiogenic drugs with radiation has been successfully studied in other cancer subtypes. Therefore, studies investigating the combination of internal radiation (yttrium-90) plus sorafenib or stereotactic body radiation therapy plus sorafenib make sense and data on these combination regimens should emerge over the next few years.

Summary

The treatment of patients with HCC is particularly challenging because of the array of patient-specific (medical comorbidities), tumor-specific (size, number, location, and vascular involvement), and liver-specific (parenchymal reserve) variables that impact our ability to treat patients safely and effectively. Risk stratification schemes such as the CLIP score or the BCLC staging system attempt to assess risk and better select patients. A robust liver oncology program needs multidisciplinary cooperation and established parameters that determine patient eligibility for each treatment option. This uniformity of treatment allows a program to assess cancer-specific outcomes while minimizing, as best as it can, the heterogeneity inherent to this patient population. Programs attempting to push the limits of treatment should probably do so under the umbrella of a liver transplant program willing to salvage patients with vulnerable parenchymal reserve. ■

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