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Novel Second-Line Treatments for Hepatocellular Carcinoma

Moderator



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

Discussants



Catherine T. Frenette, MD, FAST
Medical Director of Liver Transplantation
Director, Hepatocellular Carcinoma Program
Scripps Center for Organ Transplantation
Scripps Clinic/Green Hospital
La Jolla, California



Riccardo Lencioni, MD
Professor of Interventional Radiology
Vice-Chair, Clinical and Translational Research
Department of Interventional Radiology
University of Miami Miller School of Medicine
Sylvester Comprehensive Cancer Center
Miami, Florida

Abstract: There are 3 management approaches for patients with newly diagnosed hepatocellular carcinoma (HCC): surgery, locoregional procedures, and systemic therapies. For patients with early-stage tumors, an important step in the clinical decision-making process is the triage among transplant, resection, and ablation. Most current treatment guidelines recommend transarterial chemoembolization (TACE) as the standard of care for patients with intermediate-stage disease. After any locoregional treatment, there must be a multidisciplinary discussion involving an oncologist, a hepatologist, and an interventional radiologist to assess the results and discuss the next steps. It is critical to recognize the clinical and radiographic signs of progression so that patients can receive therapies that improve survival in the advanced setting. The optimal patient for systemic therapy is still active, has a good performance status, and has well-preserved liver function. Until recently, the only systemic treatment associated with an unequivocal survival benefit was sorafenib. The paradigm is now shifting, however, with data on regorafenib from the phase 3 RESORCE trial (Regorafenib After Sorafenib in Patients With Hepatocellular Carcinoma). The study showed a 2.8-month improvement in overall survival, with a 38% reduction in the risk of death. An important consideration with these systemic treatments is the proactive management of adverse events, including toxicities associated with the drugs and progression of liver disease.

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Second-Line Therapy for Patients With Hepatocellular Carcinoma

Catherine T. Frenette, MD, FAST

Medical Director of Liver Transplantation
 Director, Hepatocellular Carcinoma Program
 Scripps Center for Organ Transplantation
 Scripps Clinic/Green Hospital
 La Jolla, California

An initial diagnosis of hepatocellular carcinoma (HCC) leads to the consideration of 3 types of treatment approaches: first, surgical options; second, locoregional procedures; and third, systemic therapies. The surgical options of resection and liver transplant are potentially curative treatments. Ablative therapies (such as thermal ablations) are considered a surgical option, and they can be curative in patients with small tumors under 3 cm in size.

The selection of surgical treatment is based on the volume of the underlying tumor burden as well as the underlying liver function. For patients to be eligible for resection, they must have good liver function, as defined by Child-Pugh class A cirrhosis (Table 1),¹ and must also have minimal or no portal hypertension. This may be assessed by transjugular portal pressure measurements or by indirect indicators, such as the presence of thrombocytopenia, splenomegaly, or esophageal varices. The tumor must also be in a surgically accessible location. For liver transplant, patients must be within the Milan criteria (1 tumor less than 5 cm, or 3 tumors all less than 3 cm, without vascular invasion or extrahepatic spread).² They must also lack significant underlying comorbidities that would affect their posttransplant survival, such as underlying cardiopulmonary disease, extrahepatic malignancy, or uncontrolled infection.

Patients who are ineligible for a surgical option will receive noncurative treatment, such as locoregional therapy or systemic treatment.³ Locoregional therapies include chemoembolization and yttrium-90 (Y-90) radiation. Until recently, the only systemic option was sorafenib, which is the standard frontline treatment for patients with advanced HCC, including disease that is metastatic or involves vascular invasion. In the phase 3 SHARP trial (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol), sorafenib improved

median overall survival by 2.8 months in patients with advanced HCC and Child-Pugh class A cirrhosis who had not received previous systemic treatment.^{1,4} Patients in the study were not eligible for surgical or locoregional therapies or had experienced disease progression after receiving them. Median overall survival was 10.7 months with sorafenib vs 7.9 months with placebo (hazard ratio, 0.69; 95% CI, 0.55-0.87; $P < .001$).

Sorafenib is associated with a variable success rate. In the SHARP trial, the disease control rate was 43%. Although there are many patients who can achieve good disease control with sorafenib, at some point, all patients will eventually break through and develop relapsed or refractory disease. Until recently, there were no other treatment options for patients who progressed on sorafenib.

Second-Line Treatment

In my experience, approximately half of patients with advanced HCC are able to proceed to second-line therapy. Patients eligible for second-line treatment must have relatively good functional status and liver function to tolerate systemic treatment. Studies evaluating the benefit of systemic treatment have limited enrollment to patients with an Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 2 and with Child-Pugh class A cirrhosis. (Some smaller studies focusing on tolerability of systemic treatments have enrolled patients with Child-Pugh class B.)

Patients with advanced liver disease or Child-Pugh class C cirrhosis will not benefit from systemic treatment. In these patients, overall survival is based more on liver function, as opposed to the cancer, and is less than 3 months on average.

Table 1. Child-Pugh Classification^a

Finding	1 Point	2 Points	3 Points
Encephalopathy grade	None	Mild	Severe
Ascites	Absent	Mild to moderate	Severe, refractory
Serum bilirubin (mg/dL)	<2	2-3	>3
Serum albumin (g/dL)	>3.5	2.8-3.5	<2.8
INR	<1.7	1.71-2.20	>2.20

^aChild-Pugh class is assessed according to the following criteria: A, 5-6 points; B, 7-9 points; C, 10-15 points. When there are several test results for one test item, the lower point result is used to determine the Child-Pugh class.

INR, international normalized ratio.

Data from Lencioni R, Crocetti L. *Radiology*. 2012;262(1):43-58.¹

When to Initiate Second-Line Therapy

The diagnosis of relapsed/refractory disease—and when to initiate second-line therapy—is based on radiographic progression. It can be difficult to determine radiographic progression in HCC. An obvious indicator of progression is the development of a new lesion. Progression can be difficult to confirm in patients who experience growth of an existing tumor, especially if they have received previous locoregional therapy—which can alter the enhancement pattern of the tumor—or in patients who have infiltrative HCC that is difficult to measure. Modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria define radiographic progression as a growth of approximately 20%.⁵ In general, patients who are candidates for second-line therapy are those with a new lesion, new metastatic disease, or approximately 20% growth of the existing tumor.

The RESORCE Trial

Until very recently, the only option for second-line treatment for patients with progressive disease while receiving sorafenib was enrollment in a clinical trial. Patients who were not candidates for a clinical trial could continue treatment with sorafenib if they were tolerating it, or clinicians would sometimes discontinue sorafenib and initiate best supportive care. The paradigm is now shifting, however, based on data on regorafenib from the RESORCE trial (Regorafenib After Sorafenib in Patients With Hepatocellular Carcinoma).⁶ RESORCE was a randomized, double-blind, placebo-controlled, multicenter, phase 3 study evaluating regorafenib, an oral multikinase inhibitor, in patients with advanced HCC who were progressing while on sorafenib. The study showed a 2.8-month improvement in overall survival, with a 38% reduction in the risk of death.

The results from RESORCE are practice-changing.

After several negative studies of second-line treatments in HCC,^{7,8} RESORCE is the first to show any benefit. The trial enrolled patients who had tolerated sorafenib, but tolerability will probably not be a requirement for initiation of second-line treatment.

Adverse Events

An important consideration with these systemic treatments is the management of adverse events, including toxicities associated with the drug and progression of liver disease. As a hepatologist, I look closely for progression of liver disease and aggressively treat any new symptoms. Of note, tyrosine kinase inhibitors mildly inhibit conversion of indirect bilirubin to direct bilirubin, and can lead to an increase in bilirubin levels⁹ that does not indicate progression of liver disease. Therefore, in patients who are tolerating the medication but have an increase in bilirubin levels, I am careful to check direct and indirect fractionations, and often continue treatment despite increased bilirubin if no other signs of decompensation are present. The most important aspects of liver disease progression include new ascites, worsening uncontrolled ascites, encephalopathy, and variceal bleeding. Progression of liver disease is often a sign of cancer progression. When treating patients with HCC, it is necessary to ensure that new progression of liver disease is related to the underlying disease, and not to further decompensation caused by progression of liver cancer. In patients with new decompensation events, recent imaging is necessary to determine the cause of the decompensation and ensure that tumor progression is not the underlying cause, as this would change the overall prognosis and management of the patient.

Tyrosine kinase inhibitors are associated with adverse events such as diarrhea, hypertension, hand-foot skin reaction (Figure 1), and fatigue, any of which can be



Figure 1. Grade 3 hand-foot skin reaction.

severe if not managed proactively.¹⁰⁻¹² Before treatment begins, I discuss the possible side effects with patients and their families. I inform them of what to look for and when to call me, emphasizing that with any of these adverse events, early intervention is key to tolerability.¹³ I usually recommend that patients begin using a moisturizer on their hands and their feet twice a day even before treatment begins, as this decreases the risk of developing hand-foot skin reaction. If hand-foot skin reaction does occur, then use of a urea-based cream, avoidance of traumatizing activities, and, occasionally, dose reduction or temporary discontinuation can be helpful. I also recommend that patients obtain a blood pressure cuff, for use at home on a daily or at least weekly basis. Patients are instructed to call me with any evidence of new or worsening hypertension, which can be treated with oral antihypertensive agents. To help avoid diarrhea, I inform patients of dietary changes, such as avoiding lactose, excess caffeine, and coffee. Loperamide can be used if diarrhea does occur. Fatigue can be difficult to control. It is important to ensure that other causes of fatigue, such as hypothyroidism, depression, anemia, or mild hepatic encephalopathy, are not missed. To manage fatigue, patients may need to alter their daily routines by planning rest times or scheduling activities during the time of day that they have the most

energy. However, it is important that they continue an exercise regimen, as this can help minimize fatigue. Occasionally, pharmacologic measures such as modafinil may be required.

After patients begin treatment, I usually see them after a week to intervene early if any adverse events develop. Proactive management greatly helps patients tolerate treatment and remain on therapy longer, which is very important in this setting.

Disclosure

Dr Frenette is a member of the speakers bureaus of Bayer, Bristol-Myers Squibb, Gilead, Intercept, Valeant, and Merck. She has performed consulting for Bayer, Gilead, Intercept, Eisai, Wako, BTG, and Conatus.

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Preserving the Liver for Second-Line Treatment of Hepatocellular Carcinoma

Riccardo Lencioni, MD

Professor of Interventional Radiology
Vice-Chair, Clinical and Translational Research
Department of Interventional Radiology
University of Miami Miller School of Medicine
Sylvester Comprehensive Cancer Center
Miami, Florida

Interventional radiology treatments play a key role in the management of HCC.¹ Most therapeutic guidelines and treatment algorithms include a variety of interventional therapies. Image-guided ablation, along with liver transplant and surgical resection, is considered a curative treatment for HCC. Therefore, for patients with early-stage tumors, an important step in the clinical decision-making process is the triage among transplant, resection, and ablation. Ablation is increasingly being used as first-line therapy for patients with very small tumors—those at the very early stage of the Barcelona Clinic for Liver Cancer classification (Table 2)²—and it is the preferred approach for nonsurgical candidates with early-stage disease.

For patients whose disease is diagnosed beyond the early stage, transarterial treatment, which includes chemo-

embolization (TACE) and radioembolization with Y-90, is widely used (Figure 2). TACE is one of the most common treatments for HCC worldwide. There are different therapeutic regimens combining the ischemia achieved with arterial embolization with a highly concentrated local delivery of doxorubicin or other drugs. Randomized, controlled phase 3 trials of Y-90 have recently been completed, and results are eagerly awaited, as they will help define the role of Y-90 in the treatment algorithm.³ Most current treatment guidelines recommend TACE as the standard of care for patients with intermediate-stage disease according to the Barcelona criteria, meaning that they have large or multinodular tumors isolated to the liver with no evidence of vascular invasion or extrahepatic spread. These are the patients who benefit the most from locoregional therapy with TACE.⁴

An important aspect in the management of HCC, particularly with TACE, is the treatment schedule and point at which to discontinue. Typically, patients must be assessed for response to determine whether repeat treatment is indicated. In general, it is recommended that patients with compensated cirrhosis and intermediate HCC undergo 2 TACE procedures. In some cases, an initial TACE procedure misses the presence of collateral vessels, and therefore the patient does not achieve an objective response. Typically, these vessels may be recognized at the second intervention.

To capture the response, it is necessary to use imaging criteria that will take into account the necrosis induced by the treatment. The standard RECIST approach will fail to capture this effect because changes in tumor size occur late in the course of treatment. RECIST, like any other size-based imaging criteria, is not useful to capture the effects of any locoregional therapies.

Table 2. BCLC Classification of Hepatocellular Carcinoma

Stage	Description
Very early	PS 0, Child-Pugh A, single HCC <2 cm
Early	PS 0, Child-Pugh A-B, single HCC or 3 nodules <3 cm
Intermediate	PS 0, Child-Pugh A-B, multinodular HCC
Advanced	PS 1-2, Child-Pugh A-B, portal neoplastic invasion, nodal metastases, distant metastases
Terminal	PS >2, Child-Pugh C

BCLC, Barcelona Clinic Liver Cancer; PS, performance status.

Data from Llovet JM et al. *Semin Liver Dis.* 1999;19(3):329-338.²

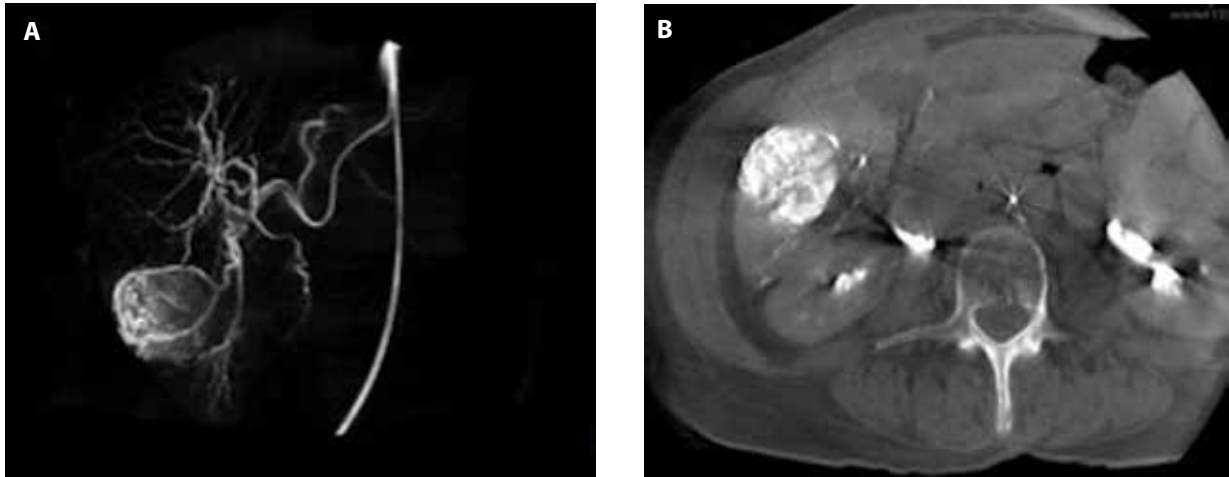


Figure 2. Current state-of-the-art intraprocedural imaging guidance for TACE. Angiographic MIP image shows hypervascular HCC tumor of segment 6 (A). Cone-beam CT confirms complete saturation of the tumor after superselective catheterization (B). CT, computed tomography; HCC, hepatocellular carcinoma; MIP, maximum intensity projection; TACE, transarterial chemoembolization.

Table 3. Conventional RECIST vs Modified RECIST Assessment for HCC

	Complete Response	Partial Response	Stable Disease	Progressive Disease
RECIST	Disappearance of all target lesions	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	Any cases that do not qualify for either partial response or progressive disease	An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started
Modified RECIST for HCC	Disappearance of any intratumoral arterial enhancement in all target lesions	At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions	Any cases that do not qualify for either partial response or progressive disease	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

HCC, hepatocellular carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors.

Adapted from Lencioni R, Llovet JM. *Semin Liver Dis.* 2010;30(1):52-60.⁵

The use of enhancement-based criteria, such as mRECIST, has been shown to reflect the antitumor effects of locoregional therapy (Table 3).⁵ This assessment is focused on the viable portion of the tumor as recognized by contrast-enhanced radiologic imaging with computed tomography or magnetic resonance imaging. Several recent studies, including a meta-analysis, have shown a clear correlation between an objective response as assessed by mRECIST after locoregional therapy and overall survival.^{6,7} Patients with an objective response benefit from the procedure, whereas those who do not

have limited survival. In the latter patients, the benefit of TACE is questionable. Therefore, an important point in the management of HCC is assessment of response.

It is necessary to focus the radiologic assessment on the territory that has been treated with TACE. In patients with tumor progression, it is important to determine whether progression, or the lack of an objective response, is related to the tumor that was treated by TACE. If progression occurs in a tumor treated by TACE, then an alternative therapy may be needed. If disease progression can be attributed to the emergence of a new HCC tumor

remote from the treated territory, then TACE may need to be used again, and directed at the new location.

The TACE procedure may impact liver function. When TACE treatment regimens are too aggressive, as reported in some randomized controlled trials conducted in the 1990s, the survival benefit may be impaired by liver decompensation. Patients with HCC have 2 diseases: the tumor and the underlying chronic liver disease. Therefore, the goal is to continue treatment as long as it is efficacious and safe, meaning that it does not impair liver function leading to hepatic decompensation and failure. This aspect of therapy is critical for this population of cirrhotic patients with HCC. It is extremely important to avoid exhausting any therapy and precluding the use of an alternative approach.

The Switch to Systemic Therapy

After TACE—as well as after any locoregional treatment—there must be a multidisciplinary discussion involving an oncologist, a hepatologist, an interventional radiologist, and any other physicians who are managing these patients to assess the results and discuss next steps and suitable options. When patients are recognized as no longer benefiting from TACE, or when portal vein invasion is identified on imaging, radioembolization with Y-90 has been shown to be a valuable approach if the disease is still limited to the liver.³ This strategy is currently used in several centers around the world. Until recently, the only systemic treatment associated with an unequivocal survival benefit was sorafenib.⁸ The RESORCE trial has now provided evidence that regorafenib is also capable of improving survival in patients who progress on sorafenib.⁹ Most guidelines and treatment recommendations, including the Barcelona scheme,² list sorafenib as the standard approach for patients with advanced-stage disease who are unsuitable for locoregional therapy. A key step in the

clinical decision-making process is to understand when to shift patients from a locoregional approach to a systemic treatment.

The RESORCE trial showing the survival benefit of regorafenib as second-line therapy in patients who progressed on sorafenib has shown, for the first time, that there may be a treatment plan in place for patients with advanced disease or who progress after locoregional therapy, and who are still candidates for systemic therapy.⁹ There is an opportunity to continue to offer these patients 2 different lines of therapy that have been shown to significantly prolong survival.

Disclosure

Dr Lencioni is a consultant for Bayer, Guerbet, and BTG.

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Developing a Treatment Plan for Hepatocellular Carcinoma: The Continuum of Care

Richard S. Finn, MD

Associate Professor of Medicine
Division of Hematology/ Oncology
Geffen School of Medicine at UCLA
Los Angeles, California

The natural history of liver cancer is such that unless patients receive curative treatment, such as surgical resection or transplant, or they die of their underlying liver disease, they will eventually develop advanced disease. A patient's disease stage at diagnosis provides insight into the prognosis and appropriate treatment modalities available to him or her. Although many patients present with early-stage disease according to tumor burden, their liver dysfunction will preclude a curative approach. These patients might be listed for transplant but not undergo the procedure because organs are not available or the tumor progresses beyond the accepted criteria. The majority of patients in the clinic present with intermediate disease (Barcelona Stage B). These patients often present with multifocal disease within the liver or had earlier-stage disease that recurred after treatment with radiofrequency ablation or surgical resection. In these patients, locoregional therapies have been shown to improve outcomes.

Locoregional Therapies

Locoregional approaches include chemoembolization with or without radiofrequency ablation to manage the disease in the liver.¹ Locoregional therapy can initially control disease in patients who present at an early or intermediate stage. Often these patients have well-compensated liver disease (Child-Pugh A liver function) or mild liver dysfunction (Child-Pugh B).

Although locoregional therapies can improve survival, they are not curative. They have a very high recurrence rate and progression rate. Patients who do well on locoregional therapy have disease that is confined to the liver. These patients generally do not have macrovascular invasion or significant symptoms from the cancer. Over

time, if a patient does not succumb to liver failure or another medical illness, he or she will likely develop a contraindication to continued locoregional therapy. These contraindications include the development of extrahepatic disease or vascular invasion. At that point, the disease has stage-migrated to a more advanced condition (Barcelona Stage C). In addition, there are patients who present with advanced disease, meaning they have macrovascular invasion or extrahepatic spread at presentation.

Physicians must understand the limits of locoregional therapy. Patients treated with locoregional therapy should undergo regular follow-up to ensure timely consideration of other treatment opportunities, including therapies that improve survival in the advanced setting.

Transition to Systemic Treatment

Once patients begin frontline therapy, the question becomes: when do they transition to second-line treatment with systemic therapy? Patients with intermediate disease become candidates for systemic treatment when they stage-migrate to more advanced disease. It is important to closely follow patients with early or intermediate disease to find a window of opportunity when they develop advanced disease but are still candidates for systemic treatment. For systemic treatment to be an option, the disease cannot be too advanced, such that they have decompensated liver function or a poor performance status. The optimal patient for systemic therapy is still active, has a good performance status, and has well-preserved liver function. These patients can tolerate systemic treatment and ultimately benefit from it.

It is critical to recognize the clinical or radiographic signs of progression. That has changed now that we have

Table 4. Clinical Trials for Advanced HCC

Trial	Drugs	Molecular Targets (signaling pathways)	Design	n	Time to Tumor Progression (months)	Median Overall Survival (months)	HR	P Value
SHARP ²	Sorafenib vs placebo	BRAF, VEGFR1-3, PDGFR- β , RAF-1 ²	Superiority	299 vs 303	5.5 vs 2.8	10.7 vs 7.9	0.69	.001
Asian-Pacific ⁴	Sorafenib vs placebo	BRAF, VEGFR1-3, PDGFR- β , RAF-1 ²	Superiority	150 vs 76	2.8 vs 1.4	6.5 vs 4.2	0.68	.01
RESORCE ⁷	Regorafenib vs placebo	VEGFR1-3, PDGFR- β , FGFR1, KIT, RET, BRAF ⁸	Superiority	379 vs 194	3.2 vs 1.5	10.6 vs 7.8	0.62	.001

Abl, Abelson tyrosine kinase; BRAF, v-raf murine sarcoma viral oncogene homolog B1; DDR, discoidin domain receptor; Eph2A, ephrin type-A receptor 2; FGFR, fibroblast growth factor receptor; RET, rearranged during transfection; PDGFR, platelet-derived growth factor receptor; PTK, protein tyrosine kinase; TrkA, tropomyosin receptor kinase A; SAPK, stress-activated protein kinase; VEGFR, vascular endothelial growth factor receptor.

data for regorafenib, which is the first new agent in liver cancer in nearly 10 years. Whereas in the past, there was a sense that systemic treatment was a “last resort” option, now that there are data on the sequential use of systemic agents—both of which improve overall survival—we must try to capture the patients who will benefit from this approach.

Systemic Approaches: Sorafenib and Regorafenib

Sorafenib, a multikinase inhibitor to the vascular endothelial growth factor (VEGF) receptor, the RAF kinase, and other cellular kinases, has repeatedly improved survival in phase 3 analyses.²⁻⁴ Sorafenib is not a cure, but it slows progression and, by doing so, helps patients live longer. In 2008, the SHARP study showed that sorafenib improved median survival by approximately 3 months (10.7 months with sorafenib vs 7.9 months with placebo; Table 4). Sorafenib also increased time to progression. It is important to time the switch to sorafenib correctly. Sorafenib does not induce significant tumor shrinkage in most patients, but typically, it slows tumor growth. Usually, there is not a real radiographic response, as seen with cytotoxic agents.

Despite many efforts to improve on these data in both the frontline and second-line settings, nothing succeeded until regorafenib. Like sorafenib, regorafenib is a multikinase inhibitor. It hits many of the same targets as sorafenib, including the VEGF family among others. Unlike sorafenib, regorafenib also targets the important angiogenic pathway mediated by TIE2. It has superior

activity against the fibroblast growth factor receptor and c-KIT. Regorafenib has activity in and is approved in other cancer types, including colorectal cancer and gastrointestinal (GI) stromal tumors.^{5,6}

Data suggest that systemic treatment improves survival in both the frontline and second-line settings in HCC. In order to position patients within this continuum of systemic treatment, it is important to individualize care. Sorafenib and regorafenib have similar adverse events, most commonly hand-foot reaction, as well as GI toxicity. Hypertension, a class effect, is somewhat more prominent with regorafenib, likely reflecting this agent's more potent antiangiogenic activity.

Sorafenib and regorafenib have been evaluated in patients with good liver function. In order to improve survival in patients with HCC, it is important to assess not only tumor burden but also the patient's functional status and the physiologic status of the liver. Patients who present with an initial diagnosis of advanced disease are often very sick, with a classification of Barcelona Stage D, and are not candidates for systemic treatment. However, patients who have an advanced tumor burden but preserved liver function and performance status are considered good candidates for such treatment. For these patients, the treatment continuum now includes first-line management with sorafenib and, at the time of progression, transition to regorafenib.

The RESORCE Trial

The RESORCE study defined clear inclusion criteria for participation.⁷ Patients had to tolerate sorafenib

treatment for a prespecified period of time and had to be progressing on sorafenib, defined as development of a new lesion while on treatment or new growth in existing tumor burden based on the RECIST criteria: at least a 20% increase in the sum of tumor diameter from the beginning of treatment or the nadir of tumor size (the maximum response).

Patients in the RESORCE trial received 160 mg/day of regorafenib for 3 weeks on and 1 week off. There was some concern about how well patients would tolerate regorafenib in the clinical context of second-line liver cancer. However, an important aspect of RESORCE is that it enrolled patients who had tolerated sorafenib. Patients had received at least 400 mg/day for at least 20 days or the previous 28 days before study enrollment. Selection of patients who tolerated sorafenib increased the likelihood of tolerance to regorafenib. In addition, patients in the study were likely being managed by clinicians who were familiar with the adverse events associated with this class of agents. As in the SHARP study, a large percentage of patients had extrahepatic disease, macrovascular invasion, and cirrhosis, but all were Child-Pugh A. Overall survival was 10.6 months with regorafenib vs 7.8 months with placebo (hazard ratio, 0.63). Remarkably, this improvement was similar to that seen in the frontline setting with sorafenib. Progression-free survival was doubled, from 1.5 months with placebo to 3.1 months with regorafenib. Regorafenib also improved time to disease progression to 3.2 months, compared with 1.5 months with placebo (hazard ratio, 0.44; 95% CI, 0.36-0.55).

With regorafenib, there is now a therapy proven to improve survival after progression on sorafenib for this population of patients. Similar to sorafenib, with regorafenib, the majority of patients gained their benefit from tumor control and slowing progression. There was a slightly higher response rate with regorafenib in the RESORCE study than was seen in the sorafenib studies. In the SHARP study, sorafenib was associated with partial response in 2% and stable disease in 71%. (There were no complete responses.) In the RESORCE trial, the disease control rate was 65.7% by RECIST 1.1 as compared with 34.5% among patients in the placebo arm. This includes a partial response rate of 6.6% by standard RECIST. Using mRECIST, the partial response rate rises to 10%.

The toxicities with regorafenib are similar to those of sorafenib: hand-foot skin reaction, fatigue, and diarrhea. Importantly, in the RESORCE trial, there was no

difference from placebo in liver dysfunction, and approximately half of patients were able to tolerate the full dose of regorafenib. The average daily dose was 144 mg/day. The actual daily dose was 160 mg/day for approximately half the patients and less than 160 mg/day for the other half.

In the colorectal cancer setting, regorafenib is often used in patients who have been heavily pretreated with prior chemotherapy,⁵ which potentially makes them less able to tolerate the side effect profile of regorafenib. Some were surprised to see that in the RESORCE trial, regorafenib was tolerable in the second-line setting in a population of patients with advanced liver cancer. This finding indicates the importance of selecting the right group of patients to start treatment not only in the second-line setting, but also in the frontline setting. Continued improvement in overall survival is unlikely, unless the right patients are selected for treatment. Optimizing outcome requires identifying patients as they transition from intermediate disease to advanced disease, and starting them on systemic therapy sooner rather than later.

Disclosure

Dr Finn is a consultant for Bayer, Novartis, Pfizer, and Bristol-Myers Squibb.

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Novel Second-Line Treatments for Hepatocellular Carcinoma: Discussion

Catherine T. Frenette, MD, FAST, Riccardo Lencioni, MD, and Richard S. Finn, MD

H&O How do you match patients with the right therapy?

Catherine T. Frenette, MD, FAST When considering any type of treatment for these patients, whether it is surgical therapy, locoregional therapy, or systemic therapy, multiple studies have shown that the use of a multidisciplinary tumor board prolongs survival and helps maintain appropriate treatment. A common mistake is for one physician to manage the patient, thereby precluding benefits offered by other specialists. For example, I work closely with an oncologist; I manage the liver disease while the oncologist administers systemic therapy for the carcinoma. I work closely with my interventional radiologist to determine whether further locoregional therapy is warranted, or whether it is more important for the patient to begin systemic treatments.

There is an appropriate time to move patients from locoregional treatments to systemic therapies, and then from one systemic therapy to the next. Physicians should not continue a certain treatment if the response is inadequate.

H&O How are adverse events managed?

Catherine T. Frenette, MD, FAST Sorafenib has been associated with different toxicity profiles in different patient types. The adverse events seen in patients with HCC differ in severity from those seen in renal cell carcinoma and thyroid cancer.^{1,2}

There has been experience with regorafenib in the colorectal setting. I expect that regorafenib will have different tolerability in HCC as compared with metastatic colon cancer. In the RESORCE study, the incidence of grade 3/4 adverse events was lower than in the CORRECT colorectal cancer study.^{3,4} The tolerability must be considered in terms of what kind of patient population that is receiving the treatment.

H&O Can locoregional and systemic therapies be combined in patients with intermediate or advanced disease?

Riccardo Lencioni, MD Several studies, particularly the SPACE (Sorafenib or Placebo in Combination With TACE) randomized clinical trial, have provided evidence that locoregional treatments such as TACE can be used in the setting of a concurrent systemic regimen with sorafenib.⁵ In fact, such a combined approach was generally well-tolerated and did not result in any new or unexpected adverse events. However, the efficacy signal captured by these studies was very modest. This field remains a very active area for research, as new drugs and novel combination approaches are currently being investigated, including the use of alternate locoregional interventions, such as radioembolization with Y-90, as well as immune checkpoint inhibitors.

H&O What are some areas of future research?

Richard S. Finn, MD There are several areas of future research. There may be the possibility of a third-line option for HCC patients. In addition, there may be an opportunity for novel combination treatments. There was not much progress with the use of sorafenib in combination. The immunotherapy agents, however, are very exciting.

Catherine T. Frenette, MD, FAST Studies are evaluating several different types of systemic therapies, including immunological therapies and other tyrosine kinase inhibitors. It will be important to determine when to move from one type of therapy. It may be possible to combine systemic treatments with locoregional or surgical approaches. It is necessary for studies to enroll the right types of patients: those with early-stage disease who are able to tolerate treatment. Patients who are frail or

sick, or who have advanced liver disease, may not be able to achieve the survival benefits seen in healthier patients, and their inclusion in studies may lead to negative results.

Disclosures

Dr Frenette is a member of the speakers bureaus of Bayer, Bristol-Myers Squibb, Gilead, Intercept, Valeant, and Merck. She has performed consulting for Bayer, Gilead, Intercept, Eisai, Wako, BTG, and Conatus. Dr Lencioni is a consultant for Bayer, Guerbet, and BTG. Bayer, Bristol-Myers Squibb, Novartis, and Pfizer have paid fees to UCLA for Dr Finn's work as a consultant/independent contractor.

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The Natural History of Liver Cancer

- The natural history of liver cancer is such that unless patients receive curative treatment, such as surgical resection or transplant, or they die of their underlying liver disease, they will eventually develop advanced disease
- A patient's disease stage at diagnosis provides insight into the prognosis and appropriate treatment modalities available to him or her
- Although many patients present with early-stage disease according to tumor burden, their liver dysfunction will preclude a curative approach

Treatment Options for HCC

An initial diagnosis of HCC leads to the consideration of 3 types of treatment approaches:

- First, surgical options
- Second, locoregional options
- Third, systemic options

HCC, hepatocellular carcinoma

Locoregional Therapy

Locoregional therapies include:

- Image-guided ablation
- Chemoembolization
- Yttrium-90 (Y-90) radiation

Shifting From Locoregional Therapy to Systemic Treatment

- A key step in the clinical decision-making process is understanding when to shift patients from a locoregional approach to systemic treatment
- After any locoregional treatment, there must be a multidisciplinary discussion involving an oncologist, a hepatologist, an interventional radiologist, and any other physicians who are managing these patients to assess the results that have been achieved and discuss next steps and suitable options

When to Initiate Second-Line Therapy

- An obvious indicator of progression is the development of a new lesion
- Progression can be difficult to confirm in patients who experience growth of an existing tumor, especially if they have received previous locoregional therapy
- mRECIST criteria define radiographic progression as a growth of approximately 20%¹
- In general, patients who are candidates for second-line therapy are those with a new lesion, new metastatic disease, or approximately 20% growth of the existing tumor

mRECIST: modified Response Evaluation Criteria in Solid Tumors.
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Candidates for Second-Line Treatment

- The optimal patient for systemic therapy is still active, has a good performance status, and has well-preserved liver function
- Patients with advanced liver disease or Child-Pugh C cirrhosis will not benefit from systemic treatment

Systemic Options

Sorafenib

- The standard frontline treatment for patients with advanced HCC, including disease that is metastatic or involves vascular invasion¹

Regorafenib

- Recently shown to improve overall survival by 2.8 months, with a 38% reduction in the risk of death compared with placebo, in patients who were progressing while on sorafenib²

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Sorafenib and Regorafenib

Trial	Treatment	Overall Survival (months)	P Value
SHARP ¹	Sorafenib vs placebo	10.7 vs 7.9	.001
Asian-Pacific ²	Sorafenib vs placebo	6.5 vs 4.2	.01
RESORCE ³	Regorafenib vs placebo	10.6 vs 7.8	.001

1. Llovet JM et al. *N Engl J Med*. 2008;359(4):378-390. 2. Cheng AL et al. *Lancet Oncol*. 2009;10(1):25-34. 3. Bruix J et al. ESMO GI abstract LBA-03. *Ann Oncol*. 2016;27(suppl 2):i140-i141.

Toxicities Associated With Systemic Treatment: Hand-Foot Skin Reaction

- Recommend that patients begin using a moisturizer on their hands and feet twice a day even before treatment begins, as this decreases the risk of hand-foot skin reaction
- If hand-foot skin reaction does occur, then use of a urea-based cream, avoidance of traumatizing activities, and, occasionally, dose reduction or temporary discontinuation can be helpful

Toxicities Associated With Systemic Treatment: Hypertension, Diarrhea, Fatigue

- Patients should obtain a blood pressure cuff, for use at home daily or at least weekly. Patients are instructed to call their physician with any evidence of hypertension
- To minimize diarrhea, patients should avoid lactose, excess caffeine, and coffee. Loperamide can be used if diarrhea does occur
- To manage fatigue, patients may need to alter their daily routines by planning rest times or scheduling activities during the time of day that they have the most energy. However, it is important that they continue an exercise regimen, as this can help minimize fatigue

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