Hepatocellular Carcinoma™

Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

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Roundtable case discussion and faculty interviews

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STATEMENT OF NEED/TARGET AUDIENCE
Emerging clinical trial data in the systemic management of hepatocellular carcinoma (HCC) have been sparse over the past few decades. However, recent breakthroughs in the understanding of the pathogenesis of this malignancy and the advent of small-molecule targeted signal transduction inhibitors and anti-angiogenesis agents have led to the development of a number of innovative clinical protocols and ongoing clinical trials. It is hoped that the results from these trials will lead to the emergence of new therapeutic agents and changes in the indications for the limited existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist and gastroenterologists specializing in liver disease must be well informed of these advances. To bridge the gap between research and patient care, Hepatocellular Carcinoma Update will use a mix of one-on-one interviews with leading oncology investigators and case-based discussions between clinical investigators and practicing oncologists. By providing access to the latest research developments and expert perspectives on the disease, this CME program will assist medical oncologists and select gastroenterology specialists in the formulation of up-to-date clinical management strategies.

GLOBAL LEARNING OBJECTIVES
• Discuss the pathophysiology and epidemiology of hepatobiliary cancer, with a focus on HCC.
• Review the primary management strategies for localized and/or resectable tumors.
• Understand the biologic rationale for the limited effectiveness of chemotherapy in patients with advanced HCC.
• Critically evaluate the clinical implications of emerging clinical trial data, including those presented at the 2007 ASCO annual meeting in HCC, and incorporate these data into management strategies in the locally advanced, relapsed and metastatic settings.
• Describe the ongoing trials examining the safety and efficacy of novel multikinase inhibitors and anti-angiogenic agents used as monotherapy or in combination with traditional chemotherapy for the current and future management of advanced HCC.
• Counsel appropriately selected patients about the availability of ongoing clinical trials.

PURPOSE OF THIS ISSUE OF HEPATOCELLULAR CARCINOMA UPDATE
The purpose of Issue 1 of Hepatocellular Carcinoma Update is to support these global objectives by offering the perspectives of Drs Geller, Roberts and Venook on the integration of emerging clinical research data into the management of hepatocellular carcinoma.

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IN THIS ISSUE OF HEPATOCELLULAR CARCINOMA UPDATE

- Review of the epidemiology, etiology and approaches to treatment of hepatocellular carcinoma (HCC)
- Role of prognostic factors in treatment decision-making
- Management approach for patients intended for liver transplantation
- Results and clinical implications of the Phase III Sorafenib HCC Assessment Randomized Protocol (SHARP) trial evaluating sorafenib versus placebo in advanced HCC
- Phase II trial evaluating doxorubicin with or without sorafenib in advanced HCC
- Systemic therapy based on Child-Pugh status
- Surgical issues in HCC resection

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A 75-year-old man with a hepatic mass on CT scan and an alpha fetoprotein (AFP) level of 345 ng/mL. Hepatitis serology was negative. The patient underwent resection for a 10-cm, moderately differentiated HCC in the right lobe of a noncirrhotic liver, with negative margins and no lymphovascular or perineural invasion (from the practice of Dr Harwin).

**DR LOVE:** Lewis, how does this case fit into the epidemiology of the disease?

**DR ROBERTS:** It tells us that one of the main messages about HCC in the United States is that a substantial proportion of the patients don’t have any risk factors for liver disease. It’s the minority, but it’s still a significant minority. In Minnesota, it’s probably 20 to 30 percent of the patients. The data from Dr Hashem El-Serag, who’s conducted nationwide studies, indicate that depending on where you are, it’s between 15 and 50 percent of the patients (El-Serag 2007).

**DR LOVE:** Alan, what is this patient’s risk of recurrence?

**DR VENOOK:** One of the main issues with HCC is not so much recurrence or metastatic disease but new primaries in the diseased liver — and he doesn’t have a diseased liver. He probably has better than a 50 percent chance of being rendered disease free.

**DR LOVE:** Would you consider sorafenib as adjuvant therapy for a patient like this?

**DR VENOOK:** Given sorafenib’s mechanism of action and demonstrated efficacy, it might be appealing theoretically. However, every drug has potential side effects, and because we have no data on whether it decreases the risk of recurrence or prolongs disease-free survival for patients with resectable tumors, I would not use sorafenib in this case.

**DR LOVE:** Would you present it as an option to this patient?

**DR VENOOK:** Yes. Sorafenib has a favorable toxicity profile. However, we don’t know what will happen to a patient who lives for 10 years after resection and receives a year of sorafenib.

I am concerned that downstream consequences may result from perturbing growth factors. Although I would mention this agent to such a patient — and most of the patients in my practice would mention it to me because they would have done their Internet search already — I would be pretty steadfast in not recommending it.
A 62-year-old man presented to the emergency room with an acute abdominal crisis and was found to have a ruptured hepatic tumor for which he underwent a right hepatic lobectomy. Pathology revealed a 5-cm HCC, with bridging fibrosis and undiagnosed cryptogenic cirrhosis. His AFP declined from 450 ng/mL to below 10 ng/mL after surgery.

Two months later, his AFP increased abruptly to the 20 to 30 ng/mL range, and a triphasic CT scan revealed subcentimeter “blushes” in the left lobe. He was started on sorafenib, and four weeks into treatment his AFP declined to 16 ng/mL (from the practice of Dr Geller).

- **DR LOVE:** David, what’s your treatment plan for this patient moving forward?

- **DR GELLER:** We are seeing a response to the sorafenib, without any side effects or complications. We are following him on protocol every three months with CT scan and AFP measurement. If he develops evidence of disease progression, with visible growth of his liver masses, then we will treat with chemoembolization in the left lobe of the liver as the next phase of treatment.

Obviously, a ruptured HCC brings a terrible long-term prognosis, but he is a fairly healthy man. Even though he has mild cirrhosis, his liver function is normal. I believe he has enough hepatic reserve to tolerate treatment, hopefully for several years.

- **DR VENOOK:** How long will you treat this patient with sorafenib?

- **DR GELLER:** I am not sure. We’ll base that decision on imaging and AFP.

- **DR LOVE:** Alan, can you comment on the findings from the SHARP trial?

- **DR VENOOK:** This was a randomized Phase III study that evaluated sorafenib versus placebo in approximately 600 patients with Child-Pugh A hepatocellular liver disease and HCC (Llovet 2007; [1.1]).

The primary endpoints were overall survival and time to symptomatic progression. At the planned interim analysis, the overall survival data dramatically favored sorafenib over placebo, the median being 10.7 versus 7.9 months, and there was also an advantage in progression-free survival.

When you have a significant \( p \)-value, it could be because the experimental treatment is effective or because patients on the control arm fare particularly poorly. In this case, patients on the control arm fared well, perhaps even better than expected for these patients, so this is a meaningful finding.

- **DR LOVE:** What about the other primary endpoint, time to symptomatic progression?
**DR VENOOK:** No difference was apparent in time to symptomatic progression, but they used a quality-of-life instrument that is difficult to use in this population of patients. In fairness, this was an early observation, and at the end of the day, the overall survival is a powerful finding.

**DR LOVE:** What were the characteristics of the patients who participated in the SHARP trial?

**DR VENOOK:** The patients were fit, by definition. Fewer than half the patients had underlying hepatitis. A quarter had alcoholic liver disease, and a quarter had other liver disease. The data were profound and the findings are important, but I am a bit concerned about how patients with hepatitis, for example, will tolerate this treatment.

### 1.1 The SHARP Trial: Efficacy of Sorafenib or Placebo in Patients with Advanced Hepatocellular Carcinoma

<table>
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<tr>
<th></th>
<th>Sorafenib N = 299</th>
<th>Placebo N = 303</th>
</tr>
</thead>
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<tr>
<td>Median overall survival</td>
<td>10.7 months</td>
<td>7.9 months*</td>
</tr>
<tr>
<td>Median time to progression</td>
<td>5.5 months</td>
<td>2.8 months†</td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>7 (2.3%)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>211 (71%)</td>
<td>204 (67%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>54 (18%)</td>
<td>73 (24%)</td>
</tr>
</tbody>
</table>

* *p = 0.000058 (HR = 0.69; 95% CI, 0.55 to 0.88)
‡ *p = 0.000007 (HR = 0.58; 95% CI, 0.44 to 0.74)


### 1.2 Child-Pugh Classification

<table>
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<th>Chemical and biochemical parameters</th>
<th>Scores (points) for increasing abnormality</th>
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</thead>
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<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy (grade)</td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt;3.5</td>
</tr>
<tr>
<td>Prothrombin time prolonged (seconds)</td>
<td>1-4</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>1-2</td>
</tr>
<tr>
<td>For primary biliary cirrhosis</td>
<td>1-4</td>
</tr>
</tbody>
</table>

Class A (good operative risk) = 5-6 points
Class B (moderate operative risk) = 7-9 points
Class C (poor operative risk) = 10-15 points

DR LOVE: Alan, how would you treat patients with Child-Pugh B, as opposed to Child-Pugh A, HCC?

DR VENOOK: I imagine the FDA will approve sorafenib for patients with Child-Pugh A disease, which will be the new standard. As for Child-Pugh B disease, the SHARP trial provides few data, but we have no satisfactory alternatives to sorafenib (Pugh 1973; [1.2]).

The NCCN suggests that sorafenib be considered for patients with Child-Pugh B disease, although there is a paucity of data to support it (4.1, page 20).

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A 67-year-old man with a history of obesity, diabetes, hypertension and congestive heart failure and a performance status of 2 presented with abdominal discomfort. A CT scan revealed four nodules in the right and left lobes of the liver and an AFP level of 4,500 ng/mL. He had Child-Pugh B disease, based on his bilirubin, albumin and prothrombin time. He did not, however, have ascites or encephalopathy (from the practice of Dr Henderson).

DR LOVE: Alan, how would you have treated this patient with Child-Pugh B disease?

DR VENOOK: This case reflects the real world we are currently facing. The dilemma is that although this patient would have been ineligible for the SHARP trial what else can we do for him? I would tell him about sorafenib and that we do not know its safety or efficacy in a case such as his, but considering the paucity of our other options, I would consider sorafenib with all the caveats.

DR LOVE: What dose of sorafenib would you use?

DR VENOOK: CALGB presented a pharmacokinetic and Phase I trial at ASCO of sorafenib in patients with hepatic dysfunction or renal dysfunction (Miller 2007). They found that patients with elevated bilirubin levels tolerated one twelfth the usual dose of sorafenib. Rather than 400 milligrams BID, they tolerated 200 milligrams every third day and still experienced a lot of toxicity.

Most of the toxicity was worsening hyperbilirubinemia, which got better when they stopped receiving the drug. The problem is that this study included solid tumors and hematologic malignancies — not only HCC. So the reasons for these organ dysfunctions may be extremely variable and the data may not be applicable.

Indeed, it may be problematic to use sorafenib for patients with hyperbilirubinemia, so I would probably extrapolate, make an educated guess and treat this patient with 200 milligrams BID because of his bilirubin level of 2 mg/dL.
DR LOVE: Lewis, do you think that as a result of the SHARP trial, more patients will now be referred to an oncologist?

DR ROBERTS: I believe it’s important to pull together a multidisciplinary team — oncologists, pathologists, hepatologists, liver surgeons, transplant surgeons — to evaluate these patients and develop a consensus regarding the best treatment for the individual patient.

DR VENOOK: I totally agree, but that is very difficult to accomplish. We try to manage all of our cases with a multidisciplinary team, and every week we hold a liver tumor board at UCSF, during which we discuss 10 or 12 different patients.

DR GELLER: I’d like to stress to the medical oncologists that patients should be considered for referral to a liver transplant center because we would hate to miss the opportunity for a potentially curative liver transplant in the appropriate subset of patients.

HCC is a cancer that typifies having three disciplines on the front line: the medical oncologists, the hepatologists/gastroenterologists and the surgeons (liver transplant and hepatobiliary surgeons).

The medical oncologist can still treat the patient, but he or she should confer with others and obtain a consensus from a liver tumor board.

I believe this should be the standard practice and is the state of the art for managing HCC. Clinicians shouldn’t “shotgun it” solo out in the community. A dialogue is needed with the tertiary referral center, and in the US we have probably 100 liver transplant centers — most university medical centers, so just about every state has one.

SELECT PUBLICATIONS


Miller AA et al. Pharmacokinetic (PK) and phase I study of sorafenib (S) for solid tumors and hematologic malignancies in patients with hepatic or renal dysfunction (HD or RD): CALGB 60301. Proc ASCO 2007; Abstract 3538.

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Track 3  Clinical use of laparoscopic resection in patients with HCC
Track 4  Role of liver transplantation in the treatment of HCC
Track 5  Bridge therapies for patients awaiting a liver transplant
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Track 9  Evolving research strategies in HCC

Select Excerpts from the Interview

Track 3

DR LOVE: You’ve taken a leadership role in the development of laparoscopic resection of HCC. What have you learned about it?

DR GELLER: This is a growing field, and I’ve performed more than 180 laparoscopic liver resections over the past five years. Cirrhotic livers don’t tend to tolerate a major hepatic lobectomy, but laparoscopic resection is an excellent option for small peripheral tumors.

If a lesion is superficial, I can perform a laparoscopic resection, but if it’s deeper in the liver, I’ll do laparoscopic ablation. The key in cirrhosis is the laparoscopic approach. We have much less liver decompensation if we don’t open the abdomen because we don’t interrupt the collateral vessels the liver has developed.

DR LOVE: To what extent is laparoscopic intervention available across the country right now?

DR GELLER: Ablation is more readily available than resection. Resection remains the gold standard in liver cancer treatment. Resection is the gold standard because you remove all the cancer and only normal liver remains.
Laparoscopic resection isn’t widely available yet. The procedure requires considerable surgical skill. You have to be both a minimally invasive surgeon and a hepatic surgeon. For the past four years, though, I’ve been teaching courses on laparoscopic liver resection surgery, so we’re seeing growth in its use.

DR LOVE: How much of an advantage is a laparoscopic procedure to the patient?

DR GELLER: It is a huge advantage for the patient for a number of reasons. Much less stress is placed on the background liver, and the patients don’t decompensate. We do not usually see development of ascites. The procedure is less morbid for the patient, with a lot less pain. Typically, the patient stays overnight in the hospital.

I tell patients, “You’re receiving the same operation. I’m cutting in the same location with the same tumor margin. It’s simply a matter of having three or four Band-Aid®-sized incisions rather than one big incision, with much less pain and fewer postoperative complications.”

Track 5

DR LOVE: How do you approach bridge procedures for patients awaiting liver transplantation?

DR GELLER: If a patient is on the list with a predicted wait time of less than three months, then we don’t need a local temporizing procedure. However, if the predicted wait time is longer than three months, then we talk about bridge therapy — administering a treatment modality that will buy time for the patient. Four treatment modality options are available.

One bridge therapy for a small tumor would be radiofrequency ablation. The size limit for a tumor we can ablate is about four to five centimeters — so no baseballs. We can ablate marble-sized tumors and golf ball-sized tumors, and we like to stay minimally invasive, using laparoscopic or percutaneous radiofrequency ablation.

A second bridge therapy, which is also good for small tumors, is percutaneous ethanol injection. It would be injected with a fine needle, with minimal morbidity. Ethanol ablation is used more commonly in Europe.

A third bridge therapy is chemoembolization — administering microscopic sponge particles combined with intrahepatic chemotherapy via an arterial approach such as a femoral angiogram. That typically treats half the liver as a local regional therapy, depending on where the tumor is located.

A fourth bridge therapy is internal radiation therapy with yttrium-90 radioactive glass beads. We’ve treated approximately 200 patients in Pittsburgh with this approach. We’ll use one of those four bridge therapies to buy time, depending on the individual characteristics of the tumor.
DR LOVE: What are your thoughts on systemic therapy, either chemotherapy or sorafenib?

DR GELLER: Until recently, we had no proven effective systemic chemotherapy for HCC. Josep Llovet presented data at ASCO from the Phase III SHARP trial — a randomized study evaluating best supportive care versus sorafenib for patients with advanced HCC (Llovet 2007; [2.1]).

It was the first study showing a significant positive effect — survival increased from 7.9 to 10.7 months (1.1, page 6) for the patients receiving sorafenib compared to those receiving the placebo.

We have two clinical trials planned at Pittsburgh for the use of sorafenib for patients with advanced liver cancer. One is a Phase II study for patients with advanced Stage III or IV, inoperable, nontransplantable hepatomas. Those patients receive sorafenib, typically 400 milligrams twice a day, with standard chemoembolization. Three quarters of the patients we see are already at a late stage and therefore must accept a nonoperative treatment modality.

If we see improved response rates above the historical controls, then we’ll move to Phase III, which would be chemoembolization alone versus chemoembolization with sorafenib. Two randomized studies worldwide, one in Europe and one in Asia, have shown that chemoembolization is effective (Llovet 2002; Lo 2002).

Now we're planning to combine sorafenib with chemoembolization to ascertain whether we can boost response rates because, even in the best of hands, response rates to chemoembolization are only 40 percent.

### 2.1 SHARP Trial: A Phase III Randomized, Placebo-Controlled Study of Sorafenib in Patients with Advanced HCC

**Protocol IDs:** 100554, NCT00105443

**Accrual:** 602 (Closed)

**Eligibility**

- Histology-proven HCC
- Advanced HCC
- At least one measurable untreated lesion
- ECOG PS 0-2
- Child-Pugh A class
- No prior systemic treatment

**R**

**Sorafenib (400 mg PO BID continuous dosing)**

**Placebo (2 tablets PO BID continuous dosing)**

Double-blind, placebo-controlled trial; ratio 1:1

**Sources:** NCI Physician Data Query, October 2007; Llovet J et al. Presentation. ASCO 2007; Abstract LBA1.
The other Phase II study is evaluating sorafenib in the adjuvant setting, after liver transplantation. We’re able to identify certain high-risk factors for recurrence, such as multifocal tumors or the presence of gross vascular invasion on the pathology specimen.

We also conduct genotyping, in which we do a DNA microarray analysis of mutations in the cancer and are able to predict a subset of patients whose disease is likely to recur. Patients at high risk due to any of those features are placed on sorafenib following liver transplantation to study whether recurrence rates are lower than predicted by historical controls.

**DR LOVE:** Are you expecting any problems with the addition of sorafenib to the post-transplant drugs?

**DR GELLER:** In general sorafenib is well tolerated. The most frequently seen Grade III or IV toxicity in the SHARP randomized Phase III study was about an eight to 10 percent incidence of hand-foot syndrome, in addition to gastrointestinal toxicity.

**DR LOVE:** In your center, 20 to 25 percent of these patients are eligible for curative resections, but what about nationally?

**DR GELLER:** It’s less than that. We have a team of seven hepatologists and a huge hepatitis screening program through which we screen patients twice a year, and we pick up a higher incidence at an early stage. Probably only 15 to 20 percent of all tumors at the national level are caught early enough to be eligible for a surgical approach.

**DR LOVE:** What’s the potential there in terms of adjuvant therapy? If you evaluate the patients who die from HCC, what fraction of those people start out with attempts at cure and then experience a recurrence, as opposed to presenting with incurable disease?

**DR GELLER:** That’s an excellent point because we follow every patient for life. I tell patients when I’m performing a radiofrequency ablation that this has a 90 percent chance at two years of being a successful ablation or even cure at the site but that we have to screen the entire liver as a precancer condition. I tell each patient, “You have a one third chance of developing new hepatomas elsewhere in your liver in the next two-year window.” We have patients with single tumors who are cured, but that’s the minority. The majority of patients experience a recurrence.

**SELECT PUBLICATIONS**


## Tracks 1-17

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<td>Estimated number of patients with HCC presenting for potentially curative resection in the US</td>
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<td>Challenges of managing fatigue associated with liver disease and treatment with sorafenib</td>
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### Select Excerpts from the Interview

#### Track 11

**DR LOVE:** Can you discuss how the Child-Pugh classification system is used clinically?

**DR ROBERTS:** The Child-Pugh system — which categorizes liver disease into Classes A, B or C — is an attempt to grade the degree of liver dysfunction. The five components are hepatic encephalopathy, ascites, serum albumin, total bilirubin and prothrombin time (Pugh 1973; [1.2, page 6]).

We use it for all patients with liver disease. Over the past several years, a shift has occurred in our assessment of liver disease, from the Child-Pugh system.
to the Model for End-stage Liver Disease (MELD) system. The MELD system was developed by Patrick Kamath and Ray Kim at the Mayo Clinic (Kamath 2007; [3.1]).

The main distinction between the two scoring systems is that the Child-Pugh system is an 11-point scale, with scores from 5 to 15 (1.2), whereas the MELD system provides a finer gradation — the lowest score is 6 and the highest is 40. MELD uses prothrombin time, bilirubin and creatinine measures. Two potential advantages of MELD are that it allows you to make finer distinctions in terms of liver decompensation and the components are easily and much more objectively measured.

In the Child-Pugh system, it was sometimes difficult to compare different assessments of ascites, for example, or of encephalopathy — those were grayer areas.

When the qualification criteria for liver transplantation were based on the Child–Pugh classification, it was difficult to compare the grading or staging of individuals across different centers. Now, with fairly objective measuring in laboratory tests, it’s easier to make those comparisons.

### Model for End-Stage Liver Disease (MELD)

“MELD incorporates 3 widely available laboratory variables, including the international normalized ratio (INR), serum creatinine, and serum bilirubin. The original mathematical formula for MELD is: MELD = 9.57 \( \log_e(\text{creatinine}) \) + 3.78 \( \log_e(\text{total bilirubin}) \) + 11.2 \( \log_e(\text{INR}) \) + 6.43. The score can be calculated on handheld computing devices, and is available at [www.mayoclinic.org/gi-rst/mayomodel5.html](http://www.mayoclinic.org/gi-rst/mayomodel5.html).”


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**Track 14**

- **DR LOVE:** How often do you use bridge therapy to control the tumor before a transplant?

- **DR ROBERTS:** That tends to be center-dependent. Centers that do not have a long wait time — less than three months — often do not perform any bridge therapy because of the low likelihood of disease progression during the wait.

A center that has more than a six-month wait time almost certainly has to use some type of local treatment to prevent too many patients dropping off the waiting list due to progression.

- **DR LOVE:** What about systemic therapy?

- **DR ROBERTS:** To this point, systemic therapies have not been used during the wait for liver transplantation. Now that we have a therapy in sorafenib that we
know to be effective in prolonging survival, we haven’t answered the question of whether it would also be effective in the pretransplant setting.

**DR LOVE:** What do we know about the safety of having sorafenib on board during a liver transplant?

**DR ROBERTS:** Sorafenib carries a small increased risk of a couple of occurrences that are important in the transplant setting. One is bleeding. You can argue that discontinuing sorafenib for a couple days or weeks before transplant would be sufficient to reduce that risk of bleeding with the transplant.

We often know when people are close to the top of the list in a particular center. When centers estimate that they may have a liver available in a month’s time, they might move the patient closer geographically.

**DR LOVE:** What kind of local interventions might be used in that situation?

**DR ROBERTS:** The most common intervention is chemoembolization, in which we infuse a combination of a chemotherapy agent or agents with Gelfoam® beads into the arterial supply to the tumor. The other commonly used modality is radiofrequency ablation.

**Track 15**

**DR LOVE:** Can you discuss chemoembolization?

**DR ROBERTS:** Chemoembolization is administered by going in typically through the femoral artery, up the aorta and then identifying the hepatic artery.

It can be used selectively in that interventional radiologists can often identify the particular branch of the hepatic artery that supplies a tumor nodule. Then they’ll infuse into the tumor nodule a mixture of Gelfoam beads — in the range of 100 to 150 microns in size — and a chemotherapy agent or agents. We use doxorubicin and mitomycin C — other institutions use cisplatin.

The goal of using the Gelfoam beads is to occlude the vasculature that’s supplying the tumor and in a sense trap the chemotherapy within the tumor.

**DR LOVE:** Do we know that the chemotherapy adds anything?

**DR ROBERTS:** Strong evidence suggests that it does. The Barcelona Clinic Liver Cancer Group conducted a study in which patients with unresectable HCC were randomly assigned to no treatment, chemoembolization or bland hepatic artery embolization (Llovet 2002). The trial was closed early when it was clear that chemoembolization led to a survival benefit.

That occurred before the bland embolization arm crossed the point of benefit. If you compared hepatic artery embolization alone to no treatment, we don’t know whether you would see a substantial difference, but clearly chemoembolization was better than hepatic artery embolization.
DR LOVE: At this point, do you believe it’s reasonable to consider using sorafenib after transplant or resection as adjuvant therapy in a clinical setting?

DR ROBERTS: I believe it’s important to complete the studies that prove that it’s valuable. One of the challenges we have in the HCC field is that we haven’t seen many therapies that are known to be effective, particularly for patients with intermediate to advanced disease. I’ve noticed a tendency to use therapies before we have clear evidence of their benefit. Therapies become almost standard without studies being conducted that prove they’re of benefit. One of the great contributions of the Barcelona Group has been their insistence on rigorous studies that justify certain management strategies.

DR LOVE: Is there an adjuvant sorafenib trial open right now?

DR ROBERTS: There are trials open, or soon to open, of sorafenib in conjunction with chemoembolization. I don’t know of any trials of sorafenib being used pretransplant.

DR LOVE: Are there situations in which you believe it would be reasonable to use sorafenib as adjuvant therapy in clinical practice?

DR ROBERTS: I believe that for many patients who have, for example, intermediate-stage disease and are treated with chemoembolization, you could make a reasonable case for placing them on sorafenib in the absence of data. However, the impetus is on us in the oncology community to conduct the studies to prove that these interventions are helpful.

DR LOVE: What about a patient who’s had a surgical resection?

DR ROBERTS: That brings us into the realm of secondary chemoprevention. Let’s assume we have a patient with cirrhosis who undergoes a surgical resection. Even if the surgical resection is complete with wide margins, the fact that he has a cirrhotic liver and has already developed cancer once tells us that he’s at risk of developing recurrent cancer.

In fact, his risk of recurrence is about 50 percent at three years, and perhaps as high as 75 percent at five years after surgical resection.

SELECT PUBLICATIONS

Kamath PS, Kim WR; Advanced Liver Disease Study Group. The model for end-stage liver disease (MELD). Hepatology 2007;45(3):797-805. Abstract


Tracks 1-14

Track 1  Historical perspective on systemic therapy for HCC
Track 2  Treatment for patients with early-stage HCC awaiting a liver transplant
Track 3  Etiology-dependent biologic variations in HCC
Track 4  Etiology of HCC in the US and Asia
Track 5  Background and rationale for the SHARP trial
Track 6  Biologic rationale for evaluating sorafenib in HCC
Track 7  Study design and eligibility for the SHARP trial

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Track 11  Response rate with sorafenib in the SHARP trial
Track 12  Clinical use of sorafenib for patients with Child-Pugh scores of B or C
Track 13  Dosing of sorafenib in patients with HCC
Track 14  Future clinical trials in HCC combining sorafenib and other biologic agents

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Can you discuss the use of systemic therapy for HCC prior to ASCO 2007?

DR VENOOK: There was no generally accepted standard systemic therapy for HCC. In part, this was probably due to the lack of dramatic efficacy of any agent. Doxorubicin was, by default, labeled the “standard of care.”

Another reason for the lack of a good standard was that systemic chemotheraphy of HCC had been relegated to use later in the course of the disease.

With the proliferation of techniques to ablate tumors — radiofrequency ablation, transarterial chemoembolization, percutaneous ethanol — healthier patients were typically treated with those modalities. Only patients whose disease progressed despite the use of those techniques or patients who had declining liver function and were not candidates for such techniques were
treated with systemic therapy. Many of us believed that nothing was effective, or we had not treated the correct population of patients to demonstrate efficacy.

DR LOVE: To what extent had adjuvant systemic therapy been evaluated?

DR VENOOK: A couple of studies suggested a benefit from adjuvant therapy. One study from Japan evaluated a semisynthetic retinoid called polyprenoic acid (Muto 1996).

Also, some soft data suggested that interferon, in patients with hepatitis C, may prevent reinfection and clear serology and, after ablation, may diminish the risk of new HCC, but no one accepts that (Ikeda 2000). Beyond those soft data, we had no solid evidence of efficacy.

The real area of need is in that population of patients and then in a growing population of patients who are diagnosed with early-stage HCC and are waiting for a liver transplant. The trick is keeping patients suitable for transplant during the 18 months it takes, on average, for an organ to become available.

If you had a preventive agent or a static agent that could safely be used, that would have a significant impact. Previously, we had no systemic therapy for use in this situation. Chemoembolization and radiofrequency ablation were options, but little else could be done for these patients.

Tracks 5, 7-8, 11

DR LOVE: Would you discuss the results of the SHARP trial, which was recently presented at ASCO (Llovet 2007)?

DR VENOOK: SHARP was a randomized, Phase III trial conducted with patients who had Child-Pugh A scores. In the SHARP trial, 95 to 98 percent of patients were classified as having Child-Pugh A disease, which means they were particularly fit patients.

A few patients had high bilirubin levels. Since the Child-Pugh classification allocates points in five different categories, patients could have scored an extra point for a high bilirubin level and still be classified as Child-Pugh A. But these are Child-Pugh A patients with good platelet counts, good white cell counts and an excellent performance status.

The randomization was to placebo versus sorafenib at 400 milligrams twice a day in perpetuity. This study was primarily conducted in Europe, where the placebo arm was necessary because they don’t support using doxorubicin in the treatment of HCC.

Overall survival, time to symptomatic progression and time to progression were the endpoints. One difficulty of making a clear interpretation of the trial outcome is that all the data haven’t yet been substantiated.
Doctors could continue administering sorafenib, even if they observed radiographic progression, provided the patients didn’t experience symptomatic progression. It doesn’t take away from the merits of the study, but it makes sorting the results precisely a little difficult.

The planned interim analysis demonstrated a superior outcome for the patients on the sorafenib arm. Ultimately, the median overall survival was 10.7 months on the sorafenib arm versus 7.9 months on the placebo arm (1.1, page 6).

A couple of points are important. The 7.9-month survival is reasonably good for a control group of patients, and the 10.7-month survival on the sorafenib arm is high.

One interesting aspect of the data is that time to symptom progression was not significantly different between the two arms. Time to progression, radiographically, was quite different — it was almost double on the sorafenib arm compared to the placebo arm.

One of the issues that limits the SHARP trial in terms of applying it to our patients is that more than half of the study patients did not have underlying hepatitis.

Many patients had cirrhosis of alcohol or other etiology. In the United States, most patients have underlying hepatitis, and the tolerability of many drugs is dramatically altered in the presence of active hepatitis.

The response rate in the SHARP study was two percent. The benefit from sorafenib is in preventing tumor growth, which is important in hepatocellular carcinoma because patients succumb to liver failure. Tumor growth into blood vessels, for example, is a major source of morbidity and a major sign of progression.

At least in the population studied, the findings do appear to be clinically meaningful. I expect that the issue will be whether they are more meaningful or less meaningful for patients with more advanced disease.

You could reason that a patient with marginal liver disease is perhaps more vulnerable to a little tumor progression, so controlling the tumor may make more of a difference.

Or you could argue the other way: Could sorafenib be changing the course of the cirrhosis? Do these factors promote the worsening of cirrhosis? When you don’t shrink the tumor, it is difficult to pinpoint what exactly the effect is from.

One concept illustrated by the sorafenib story is that the paradigm for drug development is probably broken, or at least the conventional way of developing new agents is flawed.

This was a wake-up call to all of us — cytostatic agents may make a significant difference. The conventional wisdom is that if you do not shrink the tumor, you do not make a difference — but that may not be the case.
Dr Love: What about using sorafenib for patients with Child-Pugh B or C scores?

Dr Venook: The SHARP trial included 15 patients with Child-Pugh B scores who received sorafenib. The data suggested that patients with Child-Pugh B scores might derive the same benefit, relatively speaking, as those with Child-Pugh A scores. However, caution is advised for patients with Child-Pugh B scores and elevated bilirubin levels.

**4.1 NCCN Guidelines for Hepatobiliary Cancer: Update on the Use of Sorafenib**

“The sorafenib recommendations now include Child-Pugh Class A or B, with corresponding footnote ‘l’ that states, ‘Caution: There are limited safety data available for Child-Pugh Class B patients. Use with extreme caution in patients with elevated bilirubin levels.’ Previously, the guideline only recommended sorafenib for Child-Pugh Class A patients.”


**4.2 Phase II Trial of Sorafenib with Doxorubicin or Doxorubicin Alone in Patients with Advanced Hepatocellular Carcinoma (HCC)**

Protocol ID: NCT00108953
Accrual: 96 (Closed)

**Eligibility**
- Confirmed advanced HCC
- At least one tumor that has not been subjected to local therapy or has shown a 25 percent increase in size
- Local therapy must have been completed at least four weeks prior to baseline scan
- Child-Pugh A only and no prior systemic therapy
- ECOG PS 0-2
- No history of cardiac disease or serious myocardial dysfunction
- No CNS tumors, including metastatic brain disease
- No clinically significant gastrointestinal bleeding within 30 days prior to study entry

**Preliminary Efficacy and Safety Outcomes**

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<td>Time to progression (TTP)</td>
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<td>Overall survival (OS)</td>
<td>5.6 months</td>
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<tr>
<td>Overall response rate (CR + PR)</td>
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<td>4.3%</td>
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<tr>
<td>Grade III/IV fatigue</td>
<td>6.3%</td>
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<tr>
<td>Grade III/IV neutropenia</td>
<td>41.7%</td>
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</table>

patients in the Child-Pugh A category. The toxicity is generally tolerable, with the exception of some patients with high bilirubin levels (Miller 2007).

Practically speaking, I believe sorafenib is now the standard treatment for the patient with Child-Pugh A disease. I might be comfortable using sorafenib for the patient with Child-Pugh B disease with a normal bilirubin level (4.1). I would, however, have major misgivings about using it for patients with high bilirubin levels or Child-Pugh C scores. In fairness, a lot more studies must be conducted.

Track 13

DR LOVE: Can you discuss the trial evaluating doxorubicin and sorafenib (4.2)?

DR VENOOK: The trial was presented at the ECCO meeting in Barcelona (Abou-Alfa 2007; [4.2]). It was closed early based on data from an interim analysis that demonstrated the sorafenib/doxorubicin group fared far better than the doxorubicin-alone group.

The results demonstrate that sorafenib can be combined with other agents. That could have ramifications in many other diseases in addition to HCC.

SELECT PUBLICATIONS


Miller AA et al. Pharmacokinetic (PK) and phase I study of sorafenib (S) for solid tumors and hematologic malignancies in patients with hepatic or renal dysfunction (HD or RD): CALGB 60301. Proc ASCO 2007; Abstract 3538.


QUESTIONS (PLEASE CIRCLE ANSWER):

1. Which of the following factors is not a consideration when determining a patient’s Child-Pugh score?
   a. Age
   b. Ascites
   c. Bilirubin
   d. Encephalopathy
   e. Prothrombin time

2. Which of the following factors is NOT incorporated into the MELD classification system?
   a. Encephalopathy grade
   b. Prothrombin time
   c. Bilirubin
   d. Creatinine

3. Which of the following may be used as a bridge therapy for HCC patients awaiting a liver transplant?
   a. Radiofrequency ablation
   b. Percutaneous ethanol injection
   c. Chemoembolization
   d. Yttrium-90 internal radiation therapy
   e. All of the above

4. In the Barcelona Clinic Liver Cancer Group trial comparing chemoembolization, bland hepatic artery embolization and conservative treatment for patients with unresectable HCC, chemoembolization improved survival compared to conservative treatment.
   a. True
   b. False

5. The SHARP trial of sorafenib for patients with advanced HCC demonstrated that sorafenib significantly increased ______.
   a. Overall survival
   b. Time to progression
   c. Response rate
   d. Both a and b
   e. a, b and c

6. Most patients (95 to 98 percent) who participated in the SHARP trial had a Child-Pugh score of ______.
   a. A
   b. B
   c. C

7. In the SHARP trial, Grade III or IV hand-foot syndrome and diarrhea were reported in approximately ______ percent of the patients who received sorafenib.
   a. One
   b. Eight
   c. 20
   d. 40

8. An interim analysis of a Phase II trial presented at the ECCO meeting in Barcelona demonstrated that the combination of doxorubicin/sorafenib resulted in an overall survival of ______ months compared to ______ months with doxorubicin alone for patients with advanced HCC.
   a. 5.5, 5.0
   b. 7.1, 5.0
   c. 14.0, 5.6

9. Laparoscopic liver resection is a procedure that is widely used throughout the United States.
   a. True
   b. False

10. A Phase II trial being planned at the University of Pittsburgh will combine sorafenib with chemoembolization.
    a. True
    b. False

Post-test answer key: 1a, 2a, 3e, 4a, 5d, 6a, 7b, 8c, 9b, 10a
EVALUATION FORM

Hepatocellular Carcinoma Update — Issue 1, 2007

Research To Practice respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this Evaluation Form. A certificate of completion will be issued upon receipt of your completed Post-test and Evaluation Form.

Please answer the following questions by circling the appropriate rating:

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GLOBAL LEARNING OBJECTIVES

To what extent does this issue of HCCU address the following global learning objectives?

- Discuss the pathophysiology and epidemiology of hepatobiliary cancer, with a focus on HCC. ........................................... 5 4 3 2 1 N/A
- Review the primary management strategies for localized and/or resectable tumors ........................................... 5 4 3 2 1 N/A
- Understand the biologic rationale for the limited effectiveness of chemotherapy in patients with advanced HCC. ........................................... 5 4 3 2 1 N/A
- Critically evaluate the clinical implications of emerging clinical trial data, including those presented at the 2007 ASCO annual meeting in HCC, and incorporate these data into management strategies in the locally advanced, relapsed and metastatic settings. ........................................... 5 4 3 2 1 N/A
- Describe the ongoing trials examining the safety and efficacy of novel multikinase inhibitors and anti-angiogenic agents used as monotherapy or in combination with traditional chemotherapy for the current and future management of advanced HCC. ........................................... 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. ........................................... 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

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<th>Effectiveness as an educator</th>
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<tr>
<td>Alan P Venook, MD</td>
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OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity. ....................... 5 4 3 2 1 N/A
Related to my practice needs. .................................................. 5 4 3 2 1 N/A
Will influence how I practice. .................................................. 5 4 3 2 1 N/A
Will help me improve patient care. ........................................... 5 4 3 2 1 N/A
Stimulated my intellectual curiosity. ........................................... 5 4 3 2 1 N/A
Overall quality of material. ................................................... 5 4 3 2 1 N/A
Overall, the activity met my expectations. .................................... 5 4 3 2 1 N/A
Avoided commercial bias or influence. ........................................ 5 4 3 2 1 N/A

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☐ Yes  ☐ No

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What other topics would you like to see addressed in future educational programs?

What other faculty would you like to hear interviewed in future educational programs?

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As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

☐ Yes, I am willing to participate in a follow-up survey.  ☐ No, I am not willing to participate in a follow-up survey.

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