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Cases in Point: Risk Factors, Surveillance Strategies and Treatment Options for HCC

Proceedings from a Clinical Symposium
Held at the American Association for
the Study of Liver Diseases
2008 Annual Meeting

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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists and hepatologists involved in the management of patients with hepatocellular carcinoma.

Statement of Need/Program Overview:

In order to effectively utilize both screening and treatment tools, gastroenterologists and hepatologists, as the frontline care providers for most cirrhotic patients, need to be well versed in their application as well as the accurate staging of HCC tumors and precancerous lesions. Utilization of surgical resection as well as transplant options must also be weighed and require further educated judgment, management, and coordination from hepatology caregivers. A symposium with discussion among thought leaders in the field, outlining decision-making processes for surveillance, screening, diagnosis, and treatment would provide an excellent forum for educating clinicians regarding these complex issues. Unfortunately, only a limited number of physicians can attend a live event. A widely distributed monograph, which recounts the symposium proceedings, could potentially extend the reach of the event and provide an enduring reference to community doctors not in attendance.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Describe the risk factors for HCC and the need for screening and surveillance in at-risk populations.
2. Discuss methods for accurate staging of HCC tumors.
3. Apply staging designations to reach appropriate and effective treatment decisions and implement them across medical disciplines.

Accreditation Statement: This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and *Gastroenterology & Hepatology*.

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Cases in Point: Risk Factors, Surveillance Strategies and Treatment Options for HCC

Proceedings from a Clinical Symposium Held at the American Association for the Study of Liver Diseases 2008 Annual Meeting

HCC Incidence and Prevalence

Dr. Robert G. Gish, Medical Director of the Liver Transplant Program at California Pacific Medical Center, discussed the incidence and prevalence of hepatocellular carcinoma (HCC) and the reasoning behind the need for new therapies.

Hepatocellular carcinoma (HCC) is a common cancer that is responsible for approximately 662,000 deaths yearly worldwide, and new cases are on the rise. The age-adjusted incidence of HCC in the United States increased 2-fold between 1985 and 1998.[1] The American Cancer Society estimated that in 2008, there were 21,370 new cases, and 18,410 deaths, making HCC the fifth leading cause of cancer deaths in males.[2] The economic burden of liver cancer in the United States has been estimated from a number of different databases. Based on 392 liver cancer patients in the Surveillance, Epidemiology and End Results (SEER) database, the annual estimated cost of HCC in the United States has been reported to be $454.5 million, with a per-patient cost of $32,907. Healthcare costs accounted for 89.2% of the cost in this estimate, with the remaining 10.8% of cost due to lost productivity.[3]

The classic risk factors for HCC are infection with hepatitis B virus (HBV) or hepatitis C virus (HCV). Worldwide, 50–55% of HCC is attributable to chronic HBV and 25–30% to chronic HCV.[4] In the United States, Di Bisceglie and colleagues have reported that about two-thirds of HCC patients have either HBV or HCV infection, but that one-third of patients have no known traditional risk factors.[5] In many of these cases, a contributory factor seems to be obesity. One case-control study found that obesity (BMI greater than 30) increased the risk of developing HCC by 2-fold.[6]

There is a huge unmet need in the medical care for HCC patients. Data from the SEER database between 1987 and 2001 indicates that the one-year relative survival rate is between 22% and 32%, depending upon ethnicity, and the 5-year relative survival rate is only 8–13%.[7] Part of the problem is a function of late detection, late referrals, and non-referral of patients, but a larger part can be attributed to suboptimal care. A study from the Mayo Clinic in 2005 looked at the Multiple Cause of Death file and the Nationwide Inpatient Sample database, to examine trends in mortality and hospital service utilization related to HCC. The authors found that, in 2000, the use of more advanced therapies for HCC patients (angiography/embolization, resection, local ablative therapy, liver transplantation) in non-federal hospitals was very low (Figure 1). Similarly, a 2006 study by El-Serag and colleagues of 2,963 patients in the SEER-Medicare dataset found that only 34% of patients with single lesions of less than 3 cm

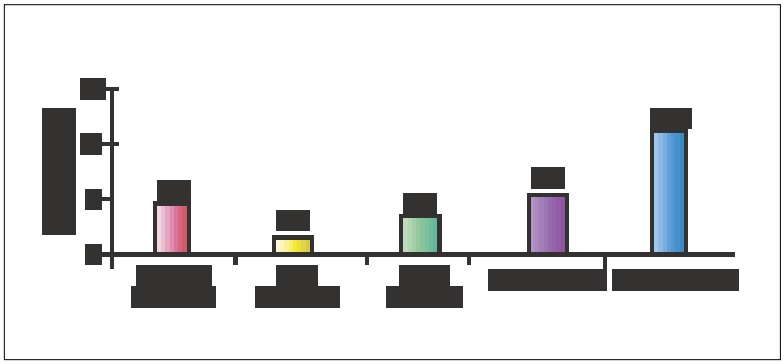

Figure 1. Treatment of HCC in US at non-federal hospitals in 2000. 2 databases evaluated for trends in HCC. Multiple Cause of Death file; Nationwide Inpatient Sample database.

Adapted from Kim WR, et al. *Gastroenterology.* 2005;129:486-493.

were offered potentially curative therapy, only 11.5% of patients who were ideal candidates for transplantation received it, and only 12.9% of patients who were ideal for surgical resection received it.[8] Because the cause of death in HCC is dominantly tumor progression,[9] halting or slowing tumor progression, resecting tumors, and ablating tumors can sometimes lead to a cure and can certainly lead to an improved outcome for a substantial number of HCC patients.

Significant Risk Factors, Surveillance Strategies, and Screening Tactics for HCC

Dr. Morris Sherman, Associate Professor of Medicine at the University of Toronto, presented data on the significant risk factors associated with the development of HCC, as well as on the efficacy of surveillance strategies and methodologies.

Significant Risk Factors for HCC

There are a number of clearly recognized risk factors for HCC. Among patients with chronic hepatitis B who are over 40 years of age, the annual incidence of HCC is 0.2%.[10] This incidence increases to 3–8% per year for cirrhotic hepatitis B carriers.[11] Similarly, patients with hepatitis C-related cirrhosis and those with stage 4 primary biliary cirrhosis have an annual incidence of 3–5%.[12-14] Alcoholic cirrhosis and nonalcoholic steatohepatitis are also risk factors for HCC, but prospective data on incidence is not available.

Within these groups of at-risk patients, there are some factors that put certain patients at even higher risk than others, and this is particularly well-studied for patients with hepatitis B. These factors include active disease, persistently elevated alanine aminotransferase (ALT) levels, low platelet count, and elevated alpha-fetoprotein (AFP) levels.[15] High levels of HBV DNA are also a risk factor for patients over the age of 35.[16,17] Dysplasia, morphologic changes, or a positive stain for proliferating cell nuclear antigen (PCNA) on biopsy also indicate increased risk.[18,19] One study has suggested that treatment with a bare-stent transjugular intrahepatic portosystemic shunt is a risk factor for HCC,[20] although further studies are needed to confirm this finding, as these patients by nature have more advanced disease.

Surveillance for HCC

Dr. Sherman opened his discussion of surveillance by proposing a question: is surveillance worthwhile? He noted that it is important to define what is meant by "worthwhile." Conventional wisdom holds that if an intervention does not enhance survival in a population by at least 3 months, it is not considered viable.[21] In addition, a 1992 study found that the 3-month improvement in survival must occur at a cost of less than $50,000 per life-year saved for an intervention to then also be considered cost effective.[22] In today's dollar, that amounts to about $72,000 per life-year saved.[23]

In regard to the first requirement, the efficacy of surveillance has been examined in a randomized controlled trial by Zhang and colleagues published in 2004.[24] They found that a semi-annual AFP test and ultrasound reduces mortality from HCC by about 37%. In this study, 18,816 people with HBV infection or history of chronic hepatitis B in urban Shanghai, China were enrolled, and half received the AFP test and ultrasound every 6 months, while the control group received no surveillance. The incidence of HCC was 223.7 per 100,000 in the screened group and 163.1 per 100,000 in the control group, for a rate ratio of 1.37 (95% CI: 0.99–1.89). The incidence was thought to be higher in the screened group because more small tumors were found among those patients. As for the comparative mortality rates, the rate of death was 83.2 per 100,000 in the screened group and 131.5 per 100,000 in the control group, which amounts to a 37% reduction in mortality for the screened group. Dr. Sherman noted that, based on these data, screening can be considered effective for patients with HBV infection, although it is difficult to know whether these results are applicable to patients with HCV infection or for those with other risk factors.

When randomized controlled trials are not feasible or the data are not available, the alternative is a sensitivity analysis, which uses plausible ranges of data to model the level of incidence that makes surveillance worthwhile in a given population. According to such a modeled cost-efficacy analysis by Sarasin and colleagues, the incidence of HCC must be at least 0.2% per year among HBV patients for surveillance to be cost-effective.[25]

So, among HBV carriers, which groups have an incidence of HCC that is at least 0.2% per year? The first group is Asian men over 40 years of age, who have an incidence of HCC of about 0.4–0.6% per year. Asian women over 50 years of age have an incidence of about 0.2% per year, and African men and women over 20 years of age have an incidence of at least 0.2% per year, although the exact figure is not known. All patients with cirrhosis would qualify for screening and subsequent surveillance, as they have an incidence of 3 to 5% per year. Lastly, any patient with a family history of HCC needs to be screened and subsequently surveilled from the time of a hepatitis B diagnosis.[21,26]

With regard to patients without HBV infection, Dr. Sherman explained that surveillance is really only performed on patients with cirrhosis, although some data do suggest that stage 3 fibrosis related to HCV may also be associated with HCC. For patients with non-hepatitis B

Table 1. Sensitivity of AFP Surveillance for HCC

Study	Sensitivity, %
Case-control studies	
Trevisani 2001	60
Surveillance studies	
Tanaka 1990	64
Pateron 1994	50
Borzio 1995	47
Sherman 1995	64
Solmi 1996	54
Zoli 1996	62
McMahon 2000	97
Bolondi 2001	41
Tong 2001	59

Trevisani F, et al. *J Hepatol*. 2001;34:570-575. Tanaka S, et al. *Cancer.* 1990;66:2210-2214. Pateron D, et al. *J Hepatol.* 1994;20:65-71. Borzio M, et al. *Gastroenterology.* 1995;108:812-817. Sherman M, et al. *Hepatology.* 1995;22:432-438. Solmi L, et al. *Am J Gastroenterol*. 1996;91:1189-1194. Zoli M, et al. *Cancer.* 1996;78:977-985. McMahon BJ, et al. *Hepatology.* 2000;32:842-846. Bolondi L, et al. *Gut*. 2001;48:251-259. Tong MJ, et al. *J Gastroenterol Hepatol*. 2001;16:553-559.

cirrhosis, modeling studies indicate that the threshold incidence for screening to be cost-effective is 1.4% per year. Which subgroups reach this threshold? As discussed previously, patients with HCV-related cirrhosis have an HCC incidence of 2–8% per year, as do patients with stage 4 primary biliary cirrhosis.[21-23] There is no data on the incidence for patients with alcoholic cirrhosis, genetic hemochromatosis, nonalcoholic steatohepatitis, alpha1-antitrypsin deficiency, autoimmune hepatitis, or cryptogenic cirrhosis.

Screening and Surveillance Methodology: Serologic Tests and Radiology

Published data indicate that currently available serological surveillance tests are insufficiently sensitive for general use. For example, the sensitivity of the AFP test in almost every population is 40–64% (Table 1).[27-35] The one exception is the Alaskan population studied by McMahon and colleagues, which is infected with a unique hepatitis B genotype; in this population, the sensitivity of the AFP screening test is 97%.[36] The specificity of the AFP test is fairly good, ranging from 82% to 95% in 6 studies, but the positive predictive value is low, 9–46% in those studies. Therefore, Dr. Sherman concluded that the AFP test is not useful as a screening test for HCC.

Combinations of serological markers have been studied for use in screening. In a prospective analysis of 99 patients with histologically proven, unresectable HCC, Couto and colleagues examined 3 prognostic markers: AFP; the Lens culinaris A-reactive fraction of AFP (AFP-L3%); and des-gamma-carboxy prothrombin (DCP). They also looked at double and triple combinations of these markers.[37] They found that each marker alone had a sensitivity of 62–72%, double marker combinations had sensitivities ranging from 74–85%, and the triple combination had a sensitivity of 86%. Dr. Sherman pointed out that although the sensitivity for double and triple marker combinations was fairly good in this study, the study population was not a screening population. All of the patients had large, unresectable HCC. When one looks at the sensitivity and specificity of the DCP and AFP tests as a function of disease stage, it becomes clear that for small tumors, these markers do not perform well enough to be used as screening tests (Figure 2). Markers of advanced disease by nature are not suited for screening purposes because screening tests serve to identify early disease.

Current serological markers are also associated with poor outcomes, including portal vein invasion, microvascular invasion, and death. Hagiwara and colleagues studied tumors from 312 patients and found that the relative risk of portal vein invasion was increased 2.5-fold for tumors that had an AFP-L3% greater than 15% when compared with those with lower levels (P=.0487).[38] In addition, tumors with a DCP level of 100 mAU/mL or greater had a 3-fold increased risk of portal vein invasion compared to those with levels under 100 mAU/mL (P=.0357). In the same study, patients with 2 or more HCC tumors had about a 5-fold increase in risk.

In another study, Shirabe and colleagues found that high DCP levels (greater than 500 mAU/mL) are associated with a 2-fold increased risk of microvascular invasion.[39] The investigators also found that tumor size over 4 cm increased risk by 3.4 fold, whereas the highest tumor grade increased risk by 2 fold. In sum, Dr. Sherman said that current serological markers are generally only useful for identifying patients with more advanced disease and for prognosis; therefore, serological markers are not recommended as a sole screening method.[40]

Computed tomography (CT) scanning has been utilized for screening purposes by some physicians; however, it has not been well-studied for screening, and there is no evidence at this point to support its use for such. For diagnosis, it is known that accurate use of CT scanning requires 4-phase contrast CT, because the false-positive rate is very high in its absence. It is also nearly impossible to distinguish small HCC tumors from dysplastic nodules or arterialized cirrhotic nodules, and flow abnormalities

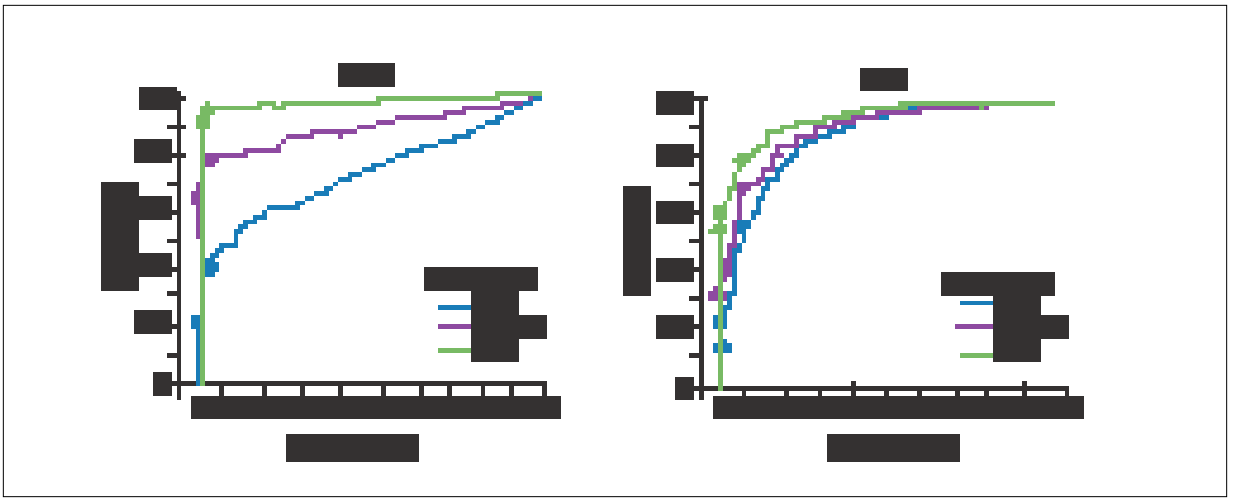

Figure 2. Sensitivity/specificity of DCP and AFP as a function of disease stage. Effect of tumor size on the diagnosis of HCC by DCP, AFP.

do create diagnostic difficulties. CT scanning also exposes the patient to a significant amount of radiation.

Ultrasound has been studied as a stand-alone screening tool. Dr. Sherman discussed work from his group that followed 2 cohorts of patients that received ultrasound screening every 6 months [J. Collier and M. Sherman, data reported at AASLD 1995]. Cohort one (n=1,005) was first followed for 5 years, during which time the sensitivity of ultrasound was found to be 79% and the specificity was 94%. The negative predictive value was 98%, but the positive predictive value was only 15%, which is rather low. Dr. Sherman's group then followed the same cohort for another 3 years, and at the same time recruited a second cohort of approximately 800 patients. Both groups continued to receive ultrasound screenings every 6 months. For cohort 1, the sensitivity and specificity during this time were both 87%, the negative predictive value was 100%, and the positive predictive value was 13%. For cohort 2, the sensitivity was 80%, the specificity was 91%, the positive predictive value was 14%, and the negative predictive value was 100%. These data indicate that ultrasound is a useful tool for HCC surveillance, and can be used as a stand-alone screening method.

The Optimal Surveillance Interval: 6 versus 12 months

Dr. Sherman next discussed selection of a surveillance interval. Choosing an interval is dependent on several factors. First, how quickly does the tumor progress from being undetectable to being detectable by the test of choice? The ideal goal is to detect tumors when they are under 2 cm. Thus, tumor growth rates would place the ideal interval between 4 and 12 months. Dr. Sherman noted that it is very important to keep in mind that the screening interval should not be chosen based upon a patient's degree of risk. Just because a patient is at higher risk does not mean the patient should be screened more often. The level of risk determines whether to screen or not to screen. Once the decision to screen has been made, screening should be performed with the best available tests and at the standard optimal interval.

What is the optimal interval? Some studies have been performed to compare 6- and 12-month surveillance intervals. Two small studies from Italy found no difference in outcome between patients screened with ultrasound at either interval. In the first study, Trevisani and colleagues retrospectively identified 821 Italian patients with cirrhosis and an eventual diagnosis of HCC.[41] The tumor was detected during semiannual surveillance in 215 patients (group 1), during annual surveillance in 155 (group 2), and as a result of symptoms or incidentally in 451 (group 3). In groups 1 and 2, the 5-year survival rate was equivalent, and it was greater in both groups than it was for group 3 ($P<.001$). In the second study, by Santagostino and colleagues, 559 HCV-infected hemophiliacs were followed at either 6-month or 12-month intervals.[42] They found that 6-month surveillance with ultrasound did not increase the chances of detection of single nodule tumors, although they noted that successful treatment of multinodular tumors was improved by the 6-month interval.

On the other hand, Kim and colleagues conducted a retrospective study among Korean patients, and they did find an advantage to the more frequent screening interval.[43] A total of 400 Korean patients who had been diagnosed with HCC between May 1990 and December 2004 via

a surveillance program of ultrasound and AFP measurement every 6 months (n=219) or 12 months (n=181) were enrolled. The investigators found that single nodular HCC was more prevalent in the semiannual group than in the annual group (90.4% vs. 72.9%, *P*<.001). The frequency of a solitary HCC tumor measuring 3 cm or smaller was also significantly higher in the semiannual group (62.1% vs. 51.5%, *P*=.003). The use of curative treatments such as resection or local ablative therapy was more frequent in the semiannual group (18.7% vs. 12.2%, *P*=.03), and the 5-year survival rate was significantly higher in the semiannual group (25% vs 16%, *P*=.006). The authors concluded that a 6-month surveillance interval results in better outcomes than a 12-month interval.

Surveillance in the United States: Current Performance

How well is surveillance being conducted in the United States? According to a study by Stravitz and colleagues[44] from Richmond, Virginia, it is not being conducted well at all. In this study, 269 patients with cirrhosis and HCC were retrospectively analyzed for quality of surveillance, tumor stage at diagnosis, and outcomes. The authors found that 172 patients had received standard-of-care surveillance (at least one abdominal imaging study in the year prior to diagnosis), whereas 48 patients received only substandard surveillance and 59 patients received no surveillance. HCC was diagnosed at tumor stages 1 and 2 in 70% of patients in the standard-of-care group, but in only 37% of patients in the substandard group and 18% of patients in the no surveillance group (*P*<.001). Liver transplantation was performed in 32% of patients in the standard-of-care group, 13% of patients in the substandard group, and 7% of patients in the no surveillance group (*P*<.001). As expected, the 3-year survival rate was very low in the no surveillance group (12%), but even substandard surveillance was better than no surveillance, with a 3-year survival rate of 27%. The standard-of-care group had a 3-year survival rate of 39%. It is clear from this study that the quality of surveillance has a direct impact on HCC stage at diagnosis, access to liver transplantation, and survival.

A second study by Davila and colleagues examined 3,093 HCC patients in the SEER database for type of surveillance received.[45] The authors defined routine surveillance to be an AFP test or ultrasound yearly for at least 2 of the 3 years prior to diagnosis. In this cohort, only 6.6% received routine surveillance; of these, 90% received AFP testing plus ultrasound, 9% received AFP testing only, and 1% received ultrasound only.

In sum, Dr. Sherman noted that at-risk patients should be screened regularly for HCC, preferably by ultrasound, and preferably at 6-month intervals. He noted that AFP testing adds cost without benefit and should be avoided.

Practical Tips for Conducting Surveillance

To finish the presentation, Barbara Sigler Morgan, MSN, RNP, added some practical points for conducting surveillance programs. First, it is important to have a protocol set up whereby standing orders for imaging studies are available in the electronic medical record. Second, it is important to utilize physician assistants, registered nurses, and registered nurse practitioners to handle a large volume of imaging reports without overburdening physicians. Clear guidelines should be set up as to what type of studies each type of practitioner can review and when to refer to the physician. Lastly, she noted that it is vital to counsel patients as to the amount of radiation exposure they will receive from CT scanning if it is used to follow up an abnormal ultrasound result, and if applicable, alternate CT scanning with ultrasound or MRI imaging methods.

Multitargeted Tyrosine Kinase Inhibitors in HCC

Dr. Al B. Benson III, of the Feinberg School of Medicine at Northwestern University, next discussed the use of multitargeted tyrosine kinase inhibitors in HCC.

HCC has a complex molecular pathogenesis. Chronic HBV or HCV infection or toxin exposure leads to cirrhosis and predisposes hepatocytes to genetic damage. This, in turn, leads to increased cellular proliferation and survival. The mechanisms include abnormal growth factor stimulation in the TGF-α and EGFR pathways, constitutively active mitogenic signaling pathways (Raf/MEK/ERK, PI3K/Akt, Wnt), dysregulated antiapoptotic signaling by p53 and PTEN, and improperly regulated pro-angiogenic signaling through the overproduction of soluble factors such as VEGF.[46]

All of these molecular abnormalities are candidate therapeutic targets, and there are several targeted agents currently under investigation in HCC. These include the EGFR tyrosine kinase inhibitors gefitinib and erlotinib, the anti-VEGF monoclonal antibody bevacizumab, and the multitargeted tyrosine kinase inhibitor sorafenib. Sorafenib is an inhibitor of the VEGFR and PDGFR tyrosine kinases as well as of Raf kinase.

Sorafenib for Advanced HCC

Initial studies with sorafenib in vitro and in mouse tumor models of HCC suggested that this agent is an effective anti-angiogenic agent, reducing mean vessel density and inducing tumor growth inhibition and tumor regression.[47] Because HCC is a hypervascular tumor, these early data soon lead to a phase II trial in patients with advanced, inoperable HCC (Child-Pugh class A or B) who had

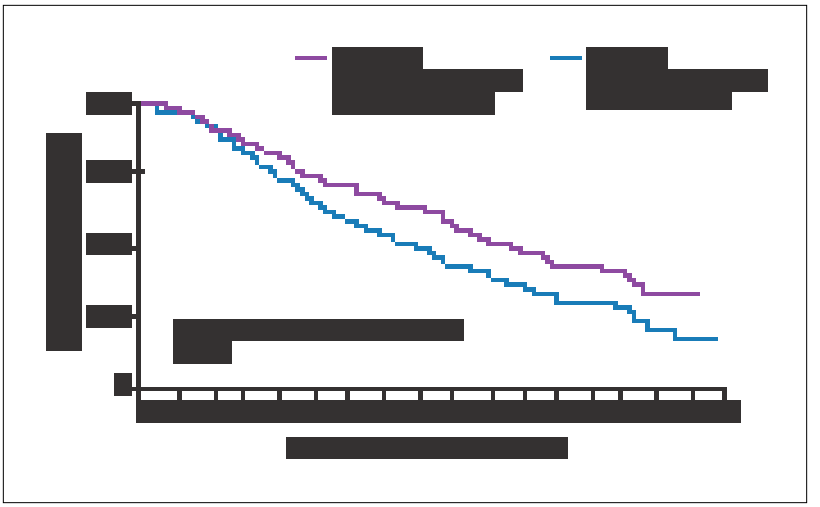

Figure 3. The SHARP Trial: overall survival.

Adapted from Llovet JM, et al. *N Engl J Med.* 2008;359:378-390.

received no previous systemic therapy.[48] A total of 137 patients received continuous sorafenib 400 mg twice daily in 4-week cycles. Tumor response was assessed every 2 cycles using modified WHO criteria. On the basis of independent assessment, 2.2% of the patients achieved a partial response (PR), 5.8% had a minor response, and 33.6% had stable disease (SD) for at least 16 weeks. The median time to progression (TTP) was 4.2 months and the median overall survival (OS) was 9.2 months. Sorafenib had an acceptable safety profile. Grade 3/4 adverse events (AEs) included fatigue (9.5%), diarrhea (8.0%), and hand-foot skin reaction (5.1%). Interestingly, the investigators found that the TTP was significantly longer for patients with higher baseline tumor cell pERK staining intensity, which they suggested might mean that tumors with higher levels of pERK may be more sensitive or responsive to sorafenib.

These data paved the way for two phase III studies of sorafenib in HCC. The first, the SHARP trial,[49] enrolled 602 patients with advanced HCC who had not received previous systemic treatment. Importantly, this trial was well-balanced for a host of factors, such as the proportion of patients with HBV-induced, HCV-induced, and alcohol-induced cirrhosis. Patients were randomized to receive either sorafenib 400 mg twice daily or placebo. The investigators found that sorafenib produced a significantly longer median OS than did placebo in this cohort (Figure 3; 10.7 months vs. 7.9 months; $P<.001$). The median time to radiologic progression was 5.5 months in the sorafenib group and 2.8 months in the placebo group ($P<.001$). There was no significant difference between the groups in the median time to symptomatic progression (4.1 months vs 4.9 months; $P=.77$). Sorafenib was found to be well-tolerated in this study. The most common grade 3/4 AEs in the sorafenib and placebo groups, respectively, were hypophosphatemia (11% vs. 2%), diarrhea (8% vs. 2%), and hand-foot reaction (8% vs. less than 1%).

The second phase III study was presented at this year's American Society of Clinical Oncology meeting by Cheng and colleagues.[50] A total of 226 Asian patients with advanced HCC, no previous systemic treatment, an ECOG performance score of 0–2, Child-Pugh class A, and a life expectancy of at least 12 weeks were enrolled. Patients were randomized 2:1 to receive sorafenib 400 mg twice daily or placebo. The median OS was significantly longer for the sorafenib group than it was for the placebo group (6.2 months vs. 4.1 months; $P=.0155$), as was the median TTP (2.8 vs 1.4 months; $P=.0007$). The time to symptomatic progression, however, did not differ significantly between groups. Again, sorafenib was found to have an acceptable safety profile. The most common grade 3/4 AEs in the sorafenib and placebo groups, respectively, were hand-foot reaction (10.1% vs 0%), diarrhea (6% vs 0%), hyperbilirubinemia (3.4% vs 2.7%) and fatigue (3.4% vs 1.3%). In regard to the difference in OS seen in the sorafenib groups between the trials, Dr. Benson noted that the Asian trial population had, on average, more tumors, greater hepatic spread, and a higher average Barcelona Clinic Liver Cancer (BCLC) stage at baseline than did the SHARP trial population.

Sorafenib has also been evaluated in combination with doxorubicin. Preliminary data have suggested greater efficacy with the combination than with sorafenib alone, and the general consensus is that these data need to have further confirmation. Therefore, the phase II trial CALGB 80802 was designed to directly compare combination treatment with sorafenib monotherapy. Eligible patients will have advanced HCC and will be Child-Pugh class A with an ECOG performance score

of 0–2. Patients will receive an initial 6 cycles of either sorafenib 400 mg twice daily on days 1–21 plus doxorubicin 60 mg/m² on day 1, or sorafenib alone. After 6 cycles, all patients will continue with sorafenib alone until withdrawal, disease progression, or death. What is interesting about this trial is that new, semi-automated imaging strategies will be used to evaluate tumor volume, including necrosis volume.

Chemoembolization for Advanced HCC

Dr. Benson then turned to a discussion of chemoembolization. The normal liver gets three-quarters of its blood supply from the portal vein and the remaining quarter from the hepatic artery, but liver tumors receive most of their blood supply from the hepatic artery. Thus, embolization of the hepatic artery along with injection of chemotherapy agents induces ischemic necrosis of the tumor and prevents systemic absorption of chemotherapy agents.

There have been a number of fairly limited studies looking at chemoembolization. One, published by Llovet and colleagues, compared chemoembolization, arterial embolization, and conservative treatment for 112 patients with unresectable HCC not suitable for curative treatment.[51] Arterial embolization was performed with a gelatin sponge, whereas chemoembolization was performed with a gelatin sponge plus doxorubicin. The primary endpoint was survival. Survival probabilities at 1 year and 2 years were 82% and 63% for chemoembolization; 75% and 50% for embolization; and 63% and 27% for control (chemoembolization vs. control P=.009).

Further comparative studies between chemoembolization, radioembolization, and bland embolization are needed to more clearly define the potential benefits for patients with HCC. One intriguing area of research is the combination of chemoembolization with sorafenib. Currently, a phase III trial (E1208) is accruing patients and is scheduled to commence in the first half of 2009 to compare treatment with transcatheter arterial chemoembolization with or without sorafenib.

Bevacizumab for Advanced HCC

Bevacizumab, a monoclonal antibody against VEGF, has been approved for use in metastatic colon cancer, non-small cell lung cancer, and metastatic breast cancer. It is currently under investigation for advanced HCC. There have been several phase II studies performed with bevacizumab, which have suggested that it can produce a disease response. Two separate phase II studies of bevacizumab monotherapy have reported a promising ORR of 13%.[52,53] Bevacizumab has also been tested in combination with chemotherapy with mixed results. A phase II study of bevacizumab in combination with gemcitabine and oxaliplatin for 30 patients with advanced HCC found an ORR of 20% and an SD rate of 27%. The median OS in this trial was 9.6 months and the median PFS was 5.3 months. Combination therapy was reported to be well-tolerated in this cohort.[54]

Whereas the gemcitabine/oxaliplatin combination appears to enhance the efficacy of bevacizumab, results have been less clear for the combination of bevacizumab with capecitabine or a triple combination of bevacizumab, capecitabine, and oxaliplatin. A phase II study of bevacizumab plus capecitabine[55] reported an ORR of 9%, whereas a phase II study using the triple combination found an ORR of 13%, similar to that seen in monotherapy trials.[56] The combination of bevacizumab with erlotinib, on the other hand, seems to be more effective than bevacizumab alone, with a reported ORR of 21% and a median OS of 19 months.[57]

Table 2. Select VEGF Multitargeted Agents Approved or in Development for HCC

Multiple agents	Multiple targets
• Sorafenib	• VEGF
• Sunitinib	• VEGFR-1
• Cediranib	• VEGFR-2
• Vatalanib	• VEGFR-3
• Pazopanib	• PDGF
• Vandetanib	• cKIT
• Brivanib	• FLT-3
• ABT-869	• RAF
• TSU-68	• RET
• Bevacizumab	• FGFR

Adapted from Verweij J, et al. *J Clin Oncol.* 2007;25:2340-2343. NCI clinical trials registry. Available at: http://www.clinicaltrials.gov. Accessed May 20, 2008.

Other VEGF-Targeted Agents in Development for HCC

There is a long and growing list of VEGF multi-targeted agents that are entering into clinical trial design for advanced HCC (Table 2). Sunitinib has been studied in phase II trials. Although it does not appear to produce disease response, it may have a disease stabilizing effect.[58] Brivanib alaninate is an oral inhibitor of the VEGF- and FGF-receptor tyrosine kinase. Dual inhibition of FGF and VEGF signaling has robust effects on HCC angiogenesis in vivo and may also impact HCC tumor growth and hepatic fibrogenesis.[59-61] An open-label phase II study performed in 54 patients with unresectable, locally advanced, or metastatic HCC showed promise for this agent.[62] Patients received 800 mg daily, which was found

to be fairly well-tolerated, with 17% of patients experiencing a serious AE. An independent review committee found a 7% PR rate and a SD rate of 49%. Computed tomography scans showed decreased vascularity and tumor shrinkage in 37% of brivanib-treated patients.

EGFR-Targeted Agents in Advanced HCC

Erlotinib, lapatinib, and cetuximab are EGFR-targeted agents that have been tested for advanced HCC. Erlotinib and lapatinib are small-molecule inhibitors of EGFR, and cetuximab is a chimeric monoclonal antibody against EGFR. Erlotinib has been approved in advanced, refractory non-small cell lung cancer and for metastatic pancreatic cancer. One early phase II trial of erlotinib in 38 patients with unresectable or metastatic HCC found an ORR of 9%, a median PFS of 3.2 months, and a median OS of 13 months.[63] In a second phase II study conducted in treatment-naïve patients with unresectable HCC, however, no responses were seen. The SD rate was 43%, the median PFS was 3.1 months, and the median OS was 10.75 months.[64] In both studies, erlotinib was reported to be well-tolerated, with 26% of patients in the first requiring a dose reduction, and no patients requiring dose reductions in the second.

Lapatinib has been approved in combination with capecitabine for advanced, metastatic breast cancer that is HER2 (EGFR) positive. One phase II study has been performed for lapatinib in advanced HCC. Among 40 patients, the ORR was 5%, the median PFS was 2.3 months, and the median OS was 6.2 months.[65]

Cetuximab has been approved for certain head and neck cancers and for colorectal cancer. In the field of HCC, 2 phase II trials have been conducted with cetuximab monotherapy, and the results were disappointing. The first trial, which enrolled 32 patients, found an ORR of zero, an SD rate of 44%, and a median TTP of 8 weeks.[66] The second trial enrolled 30 patients. The ORR was again zero, and 17% had SD. The median PFS was 1.4 months, and the median OS was 9.6 months.[67]

Much more exciting results have been found for combination therapy with cetuximab and chemotherapy. A recent phase II trial treated 45 treatment-naïve patients with a loading dose of cetuximab 400 mg/m^2 followed by a dose of 250 mg/m^2 weekly. All patients also received gemcitabine 1000 mg/m^2 on day 1 and oxaliplatin 100 mg/m^2 on day 2. The regimen was repeated every 2 weeks until disease progression, unacceptable toxicity, or patient refusal. The ORR was 20%, and 40% had SD. The median PFS was 4.7 months and the median OS was 9.5 months. The investigators found that combination therapy had manageable toxicity. Grade 3/4 thrombocytopenia was seen in 24%, neutropenia in 20%, and anemia in 4%. Grade 3 oxaliplatin-induced neurotoxicity occurred in 11% and grade 3 cutaneous toxicity in 16%. There were no treatment-related deaths. A comparative randomized trial is now being planned.[68]

Managing Adverse Events

Ms. Sigler Morgan rounded off the discussion by presenting some key recommendations for managing the potential side effects of targeted agents. One of the most common side effects of multitargeted TKIs is a hand/foot skin reaction that is characterized by tender lesions that are scaling and have a halo of erythema at pressure or flexure points. Later, areas of thickened skin develop. This reaction typically occurs within the first 2–4 weeks of treatment, and no later than day 45. The hand/foot skin reaction occurs in up to 60% of patients receiving multitargeted TKI therapy.[69-71]

Ms. Sigler Morgan listed several prophylactic measures that should be taken with these patients: perform a full-body skin exam before initiation of therapy; consider pedicures to remove calluses and hyperkeratotic regions; use orthotic devices in patients with abnormal weight bearing; counsel patients to reduce hand and foot exposure to hot water; encourage patients to rest and to avoid traumatic activity or vigorous exercise during early stages of therapy; counsel patients to avoid constrictive footwear and friction to the skin.[72] In addition, she emphasized the importance of seeing patients in the clinic in the first 2 to 3 weeks of therapy because patients often minimize the extent of skin reaction when speaking over the telephone.

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Notes

Cases in Point: Risk Factors, Surveillance Strategies and Treatment Options for HCC

CME Post-Test: *Circle the correct answer for each question below.*

1. According to a study by El-Serag and colleagues of 2,963 patients in the SEER-Medicare dataset, __% of patients with single HCC lesions of less than 3 cm were offered potentially curative therapy in 2000.

   a. 12%
   b. 34%
   c. 45%
   d. 74%

2. Which of the following is NOT a risk factor for the development of HCC in patients with chronic hepatitis B?

   a. persistently elevated ALT level
   b. low platelet count
   c. high HBV DNA level in patients under the age of 35
   d. elevated AFP level

3. According to the randomized controlled trial by Zhang and colleagues, a semi-annual AFP test and screening ultrasound in at-risk patients reduces mortality from HCC by about __%.

   a. 37%
   b. 39%
   c. 42%
   d. 56%

4. Which of the following groups qualifies for HCC surveillance?

   a. Asian men over 40 years of age
   b. African men and women over 20 years of age
   c. All patients with cirrhosis
   d. All of the above

5. True or False? Based upon current data, AFP testing alone can be considered standard-of-care for HCC surveillance.

   a. True
   b. False

6. According to the Korean study by Kim and colleagues, which surveillance interval is associated with increased 5-year survival among patients who are eventually diagnosed with HCC?

   a. 6 months
   b. 9 months
   c. 12 months
   d. 24 months

7. In the SHARP trial, sorafenib treatment produced a median OS of __ months, while the placebo group had a median OS of __ months.

   a. 10.7, 7.9
   b. 7.9, 10.7
   c. 6.2, 4.1
   d. 4.1, 6.2

8. Which of the following treatment combinations showed the longest median OS for patients with advanced HCC in phase II trials?

   a. bevacizumab, gemcitabine, and oxaliplatin
   b. bevacizumab and capecitabine
   c. bevacizumab, capecitabine, and oxaliplatin
   d. bevacizumab and erlotinib

9. Cetuximab has shown promise for the treatment of advanced HCC in combination with which chemotherapy agent or agents?

   a. gemcitabine
   b. gemcitabine and oxaliplatin
   c. capecitabine
   d. capecitabine and oxaliplatin

10. True or False? Patients beginning multitargeted TKI therapy should be monitored for side effects via telephone within the first 2 to 3 weeks; an in-office visit is not necessary.

    a. True
    b. False

Evaluation Form

Cases in Point: Risk Factors, Surveillance Strategies and Treatment Options for HCC

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

1. Describe the risk factors for HCC and the need for screening and surveillance in at-risk populations.	1 2 3 4 5
2. Discuss methods for accurate staging of HCC tumors.	1 2 3 4 5
3. Apply staging designations to reach appropriate and effective treatment decisions and implement them across medical disciplines.	1 2 3 4 5

Overall Effectiveness of the Activity

The content presented:

Was timely and will influence how I practice	1 2 3 4 5
Enhanced my current knowledge base	1 2 3 4 5
Addressed my most pressing questions	1 2 3 4 5
Provided new ideas or information I expect to use	1 2 3 4 5
Addressed competencies identified by my specialty	1 2 3 4 5
Avoided commercial bias or influence	1 2 3 4 5

Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity.

Please list any topics you would like to see addressed in future educational activities.

Additional comments about this activity.

Follow-up

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

☐ Yes, I would be interested in participating in a follow-up survey. ☐ No, I'm not interested in participating in a follow-up survey.

If you wish to receive acknowledgment for completing for this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

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