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Integrating Recent Data in Managing Adverse Events in the Treatment of Hepatocellular Carcinoma

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Abstract Hepatocellular carcinoma (HCC) is a major cause of cancer-related morbidity and mortality worldwide. In the United States, HCC is the main cause of death in patients with cirrhosis, and the incidence of this malignancy is on the rise. Because HCC is associated with a particularly poor prognosis, emphasis is placed on surveillance of high-risk patients. Early detection allows a greater chance of diagnosing HCC before it has spread, thus increasing the chances that the patient can be potentially cured with surgical techniques such as resection and transplantation. However, most cases of HCC are not diagnosed until at least some of the cancer has spread or multiple nodules exist. For these patients, treatment options include percutaneous and transarterial ablation, as well as systemic chemotherapy. Systemic therapy is now considered the standard of care for patients with advanced tumors. Traditional treatment was based on cytotoxic chemotherapeutic agents, such as doxorubicin. This approach was associated with minimal benefit and a high rate of toxicity. Recently, targeted agents have proven more effective and safer in this setting. The oral multikinase inhibitor sorafenib is now approved for the treatment of unresectable HCC and is currently the only approved agent for advanced HCC. In order to maximize the benefit of sorafenib and other investigational agents for patients with advanced disease, effective interventions have been designed to mitigate their associated adverse events, such as hand-foot skin reactions and hypertension.

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Target Audience: This activity has been designed to meet the educational needs of practicing clinicians, medical oncologists, gastroenterologists, and hepatologists involved in the management of patients at risk of or diagnosed with hepatocellular carcinoma (HCC).

Statement of Need/Program Overview: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related morbidity and mortality worldwide. Risk factors include hepatitis viral infection, certain comorbidities, and external sources. Because HCC is associated with a particularly poor prognosis, emphasis is placed on surveillance with techniques such as serologic tests and abdominal ultrasound examination. Traditional treatment of HCC was based on cytotoxic chemotherapeutic agents. This approach was associated with minimal benefit and a high rate of toxicity. Targeted agents, including the oral multikinase inhibitor sorafenib, have recently proven more effective and safer in this setting. Many staging systems exist to help physicians select the appropriate treatment for each patient. A multidisciplinary approach to management, including hepatologists, gastroenterologists, and oncologists, can maximize patient outcomes. The majority of HCC cases are first screened by a hepatologist or gastroenterologist, mainly because these physicians care for patients with chronic liver disease. The introduction of sorafenib and its use as the standard of care has enforced the role of oncologists in the treatment of HCC. Associated adverse events, such as hand-foot skin reaction, fatigue, diarrhea, and hypertension, must be managed so as not to diminish the efficacy of treatment.

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

1. Describe methods of surveillance for HCC
2. Discuss the latest data regarding treatment options for HCC
3. Identify techniques to manage the adverse events associated with HCC therapeutic agents
4. Describe the roles of the oncologist, hepatologist, and gastroenterologist in the management of HCC patients

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HCC Epidemiology and Surveillance

Myron J. Tong, MD, PhD

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide, comprising 5.7% of new cancer cases.[1] In the United States, the incidence of HCC has steadily risen since the early 1980s,[2] making it the most rapidly increasing cancer in the country. The incidence of HCC in the United States is approximately 3 cases per 100,000 people.[3] Due to its poor prognosis, it is the third-leading cause of cancer-related deaths worldwide and the ninth-leading cause of cancer deaths in the United States.[1,4]

A specific geographic distribution of HCC has been reported. Worldwide, HCC is most prevalent in areas where hepatitis B, and more recently hepatitis C, infections commonly occur.[5] Thus, the incidence of HCC appears to be more prevalent in Asian countries, such as China, Japan, Korea, and Southeast Asia, and in many countries in Africa.[5]

In the United States, the incidence of HCC is rising. Age-adjusted incidence rates from the Surveillance, Epidemiology, and End Results (SEER) registry show that the incidence of HCC tripled between 1975 and 2005.[4] This increasing incidence is present in both men and women, but it is approximately 3 times higher in men. Overall, the annual increase in HCC incidence from 1992–2005 was 4.3%. During this period, Asians/Pacific Islanders had the highest incidence of HCC, followed by Hispanics, blacks, American Indians/Alaskan natives, and whites. Interestingly, the HCC mortality rate is also affected by race, with the highest rate of death occurring among Asians/Pacific Islanders, followed by Hispanics, blacks, American Indians/Alaskan natives, and whites.

In the United States, the Asian-American population has the highest death rate due to HCC.[6] The incidence of HCC differs between Asians who were born in the United States and Asian immigrants. From 1979–1981, the incidence of HCC was higher for Asian immigrants compared with Asians born in the United States (13.8 vs 6.1 cases per 100,000 people). From 1990–2001, the incidence rate for Asian immigrants was 18.3 compared with only 6.7 cases per 100,000 Asians born in the country. During the same time period, the HCC incidence among whites rose from 3.2 to 4.8 cases per 100,000 people.

Risk Factors

A number of risk factors have been associated with HCC. The most common risk factors for the development of HCC stem from chronic viral hepatitis infection, certain comorbidities, and other causes of cirrhosis. In the United States, the major cause of HCC is hepatitis C infection, which accounts for nearly 50% of cases.[7] Hepatitis B is also a major cause, accounting for approximately 15% of cases.[8] In Asia and Africa, and in some eastern European countries, chronic hepatitis B is the leading cause of HCC.[9] Japan is unique among Asian countries in that hepatitis C is the primary causative agent for HCC.[9] In the United States, Latin America, and Europe, hepatitis C is the primary cause of HCC.[9]

Other conditions that have been found to be associated with the development of HCC include cirrhosis, alcoholic liver disease, and nonalcoholic steatohepatitis (NASH).[9] There are also less common causes of HCC, including hereditary hemochromatosis; among patients with this condition, the incidence of HCC is very high, although the condition itself is less common. Cirrhosis due to conditions such as autoimmune hepatitis or alpha 1 antitrypsin deficiency is also associated with a low incidence of HCC.[10]

Pathogenic Pathways to HCC

Hepatitis C, hepatitis B, NASH, and alcoholic liver disease all share the common characteristic of causing liver injury. After several years, this injury progresses from chronic inflammation to cirrhosis. Within the cirrhotic nodules, the tissue becomes progressively hyperplastic and then dysplastic, ultimately transforming into cancerous cells. Thus, even though the etiology may differ according to the type of liver injury, the end result follows a common pathway into HCC transformation.

HCC cells are pathologically divided according to their degree of differentiation, with the most differentiated cells appearing very much like normal liver cells. These pathologic categories include well-differentiated (the cells appear very much like normal liver cells), moderately differentiated, and poorly differentiated (the appearance of the cells is very distinct from that of normal liver cells).[11]

HCC Surveillance

Among patients presenting to the clinic with HCC, up to one-third have cancer localized to the liver only. Treatment options for patients with earlier stage disease include surgical approaches (such as liver transplant and resection) and interventional radiologic techniques (such as transarterial chemoembolization, radiofrequency ablation, and transarterial radioembolization). The remaining HCC patients have evidence of disease metastasis. The 3 most common areas of liver metastasis are the regional lymph nodes of the liver, the lung, and the bone. Unfortunately, once HCC has spread outside the liver, the treatment options for these patients become more limited.

Patients with untreated HCC who have intermediate- or advanced-stage disease have a poor prognosis. Therefore, special emphasis is placed on HCC surveillance in high-risk patients, in order to detect liver tumors at earlier stages and provide patients with the most treatment options.

The main goal of surveillance for cancer of any kind, including HCC, is to reduce the mortality rate. For HCC patients specifically, the goal is to detect small, early-stage tumors that are fewer in number and more amenable to the available treatment options. Patients with this stage of disease experience a far greater survival rate after liver transplantation and surgical resection. One of the most common tests used for HCC surveillance is the measurement of serum alpha-fetoprotein (AFP), an oncoprotein produced by liver cancer cells. The use of AFP as a surveillance tool was validated in a large, randomized study of 18,816 Chinese patients who had either hepatitis B infection or a history of chronic hepatitis.[12] AFP testing and ultrasonography every 6 months was associated with a 37% reduction in HCC-related mortality. In a community clinic setting, survival in HBV patients whose HCCs were detected by surveillance using AFP and abdominal ultrasound examination were compared to hepatitis B surface antigen–positive patients who were referred to our clinic with already diagnosed HCC.[13] Significantly more surveillance patients had normal liver tests and had smaller tumors that were within the Milan and University of Southern California San Francisco criteria. In addition, survival rates at 1, 3, and 5 years were significantly better in patients whose HCCs were detected by routine surveillance. Elevated AFP levels are detectable in 60–70% of HCC patients.[14,15] This test has been used for many years for HCC surveillance. Other serologic tests have been used for HCC, but are less commonly used around the world. These tests include the Lens culinaris agglutinin-reactive AFP (AFP-L3) and protein induced by vitamin K absence or antagonist-II (PIVKA-II).[14] Interestingly, the increase in the proportion of AFP-L3 over total AFP may detect HCC associated with smaller tumor burdens. In addition, all 3 markers may be used to monitor treatment responsiveness and tumor recurrence.

Another approach for HCC surveillance is abdominal ultrasound examination. Abdominal ultrasounds are widely available and associated with a low cost. Furthermore, these examinations can be used to detect tumors that are 1 cm in diameter. This particular modality is widely used and has been validated as a good surveillance test for HCC. However, it is not completely accurate, and it is very dependent on the quality of the ultrasound apparatus and the skills of the operator. Institutions that provide better training and employ this technique more frequently may result in more experienced operators and, therefore, offer more accurate diagnosis of liver lesions.

Imaging studies such as spiral computed tomography (CT) and magnetic resonance imaging (MRI) are not recommended for an HCC surveillance program. It is likely that these modalities would be overused, result in greater and possibly unneeded radiation exposure, and would incur an unacceptably high cost. However, once HCC is suspected—either through the results of a serum test or abdominal ultrasound—a spiral CT scan with contrast or an MRI with contrast should be used for diagnosis. If the case remains unclear even after imaging studies, a liver biopsy may be used for confirmation.

In patients at particularly high risk for HCC, such as those with cirrhosis, surveillance tests should be performed at least every 6 months.[16] Recent reports now show that this frequency improves the survival rate in this high-risk population compared to surveillance testing every 12 months. This improvement is likely due to the fact that a small tumor detected at 6 months could by 12 months develop into a much larger tumor that would be less amenable to current treatments. In the United States, patients with chronic hepatitis B only that has not progressed to cirrhosis should undergo surveillance testing every 6–12 months, due to their lower risk of developing HCC. Patients who are carriers for hepatitis B, but who have no significant liver disease, should be screened once a year, as up to 30% of HCC occurs in patients without cirrhosis. The hepatitis B viral genome can integrate into the host genome, which can increase the chance of inducing malignant changes in the liver cells. It has recently been shown that carriers of hepatitis B virus had a substantial risk of HCC compared with non-infected individuals and that elevated serum hepatitis B DNA levels (≥10,000 copies/mL) were strongly associated with the development of HCC independent of cirrhosis.[17,18] Patients with hepatitis C and advanced fibrosis or cirrhosis should also undergo surveillance testing every 6–12 months. Other patients who should undergo more rigorous screening include those with a family history of liver cancer, as they may also be at an increased risk.

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HCC Treatment Options and Their Associated Adverse Events

Robert G. Gish, MD

The Barcelona Clinic Liver Cancer (BCLC) system is frequently used to classify HCC patients. The BCLC system is unique in that it links stage with treatment indication, and does so based on robust scientific data.[1] However, other HCC "staging systems" are also widely employed, including the Japan Integrated Staging (JIS) system, the Chinese University Prognostic Index (CUPI), the National Comprehensive Cancer Network (NCCN) classification, and the Tumor, Node, Metastasis (TNM) system from the American Joint Committee on Cancer. Some of these staging systems are directly cancer-stage related, and others, such as the Child-Pugh-Turcotte score, form a composite of clinical and laboratory data. Although guidelines such as those from the NCCN do not recommend the use of one system over another, they do suggest categorizing patients according to their potential for resection or transplant, performance status, comorbidities, and evidence of metastasis.[2]

Surgical Resection

For patients presenting with HCC who have either no cirrhosis or cirrhosis at a very early stage and no evidence of portal hypertension, the standard of care is to first offer surgical resection. In patients with early-stage disease, liver resection is potentially curative. Although surgical resections are associated with a 5-year survival rate of 50%, this rate can be as high as 70% in patients with very early-stage disease.[3-7] However, the 5-year recurrence rate among patients receiving a surgical resection for HCC is also 70%.[5,8] A partial hepatectomy may be used in appropriate patients, allowing for the potential of a lower risk of surgery-associated morbidity and mortality. A few centers worldwide might consider a transplant for these patients; however, because liver organs are in such short supply, and there are little data for the success of transplanting noncirrhotic patients, resection is considered the standard of care in the United States for patients without portal hypertension.

Careful selection of patients for surgical resection is an essential step, as it helps to identify those patients who will obtain the most benefit and have the best prognosis. Patient assessment should consist of an evaluation of patient and tumor characteristics, as well as of the liver organ itself.[2] Surgical resection is only recommended for patients with preserved liver function; potential resection candidates are staged for their level of liver dysfunction and degree of portal hypertension, as both of these factors predict the risk of major complications following surgery. Optimally, HCC tumors identified for resection should be solitary with little evidence of vascular invasion. The NCCN guidelines do not identify a threshold of tumor size for surgical resection; however, the risk of vascular invasion and tumor cell dissemination is increased with greater size.[9-11]

One of the main complications associated with surgical resection is decompensated liver disease, which can present with jaundice, ascites, coagulopathy, and hepatic encephalopathy. The threshold for liver decompensation is an elevated portal hypertension of less than 12 mm Hg for the portal vein-hepatic vein gradient.

Liver Transplantation

All HCC patients should be evaluated to determine if they have the potential to be a candidate for liver transplantation. Like surgical resection, liver transplantation is potentially curative for HCC. Unlike resection, liver transplantation has the added benefit of removing undetectable liver lesions and underlying liver cirrhosis and thus increases both overall long-term survival and tumor-free survival in addition to increasing the long-term cure rate. Globally, most centers follow the United Network for Organ Sharing (UNOS) Milan criteria for selection of patients for liver transplantation. Using the Milan criteria, the 4-year overall survival (OS) and recurrence-free survival rates for carefully selected patients following liver transplantation is 85% and 92%, respectively.[12,13] However, a number of centers have expanded upon this criteria to include larger tumor size or greater tumor number. Although the use of expanded criteria is an area of active debate, these criteria have performed well in patients with more benign HCC disease.

A wide variety of complications are associated with liver transplantation. Immediate post-transplant complications include infection, primary graft nonfunction, bile duct leak, bile duct necrosis, and bile ascites, as well as pneumonia and wound infection.

The main long-term risk following liver transplant is disease recurrence. Transplant recipients who are selected based on the Milan criteria have a 15% chance of HCC recurrence at 5 years. Generally, after 30 days have passed post-transplant, HCC patients are monitored long-term for disease recurrence. In most centers, patients undergo regular surveillance measures, including ultrasound, MRI, or CT scans; CT scans of the chest and abdomen, as well as bone scans, may also be used for surveillance. Using the UNOS Milan criteria, certain tumor size and grade characteristics are associated with increased risk of recurrence. Due to the risk of tumor cell seeding, which is as low as 0% and as high as 15%, most patients do not undergo a liver biopsy before either a surgical intervention or liver transplant.[14-16] Part of the variation in the risk of tumor cell seeding is due to the technique used for the intervention. For example, a deep biopsy is associated with a lower risk compared with a superficial biopsy, whereas a fine needle aspiration has a lower risk compared with biopsy but also a lower accuracy.

Ablation

The 2 major forms of ablative therapies for HCC are percutaneous thermal ablation (through the skin) and transarterial therapies. Among percutaneous methods, radiofrequency ablation is the most common. Alternatively, microwave ablation, which has different heating characteristics, is becoming increasingly used due to much shorter procedure times and the lack of "cooling" by adjacent blood vessels. In the United States, percutaneous ethanol injection is now used only in rare situations, and cryotherapy is generally not employed due to its expense relative to the efficacy of radiofrequency ablation, its lower efficacy, and its very long operative times. Among transarterial therapies, the 2 most common forms are chemoembolization, an oil-based solution (which is not available at this time in the United States) mixed with chemotherapy (typically doxorubicin, mitomycin, or cisplatin, alone or in combination), and bead embolization. The major types of beads used for bead embolization include doxorubicin-eluting beads and yttrium-labeled glass beads. Doxorubicin-eluting beads are made of a polyvinyl chloride plastic, allowing the doxorubicin to reside within the interstices of the microbead, which is available in 3 different sizes. The most important factor for the success of bead embolization is the technique used to inject the beads. Instead of placing the beads at such a high density to result in complete stasis, a lower risk of complications occurs when the bead placement achieves a marked slowing of fluid through the tumor without complete obstruction or halting of blood flow.

Abscess formation is the major complication associated with both percutaneous ablation and transarterial ablation procedures.[17] Although it is difficult to ascertain the exact incidence of abscess formation in this setting, variable reports suggest it is in the range of 2–5%.[17-19] Abscess formation is dependent on tumor size as well as the amount of material (either beads or oil) placed into the tumor. The risk of abscess is also dependent upon whether an arterial occlusion method is employed following the primary embolic method, and risk is directly related to the amount of ischemia present. Because of the potential seriousness of abscess formation, it is important to inform the patient of this risk and to employ antibiotic prophylaxis. The antibiotic regimen is typically ciprofloxacin or ofloxacin in combination with metronidazole, administered for 5 days following the ablation procedure. For inpatients who are more ill or at greater risk of developing an infection, intravenous antibiotics may be administered for 1–3 days following the procedure.

Doxorubicin, once more widely used as an intravenous chemotherapy agent to treat HCC, has essentially been completely replaced by sorafenib and clinical trial enrollment for other systemic therapies of HCC that are in development. Doxorubicin use is associated with substantial accumulation, leading to cardiotoxicity in patients with previous cardiac dysfunction or elevated levels of bilirubin. This adverse event has limited the use of intravenous doxorubicin in HCC patients who are jaundiced or who have known cardiac or myocardium dysfunction, congestive heart failure, or low cardiac output. The systemic exposure of doxorubicin when it is used in bead embolization is very low, in contrast to that associated with intravenous administration. Because the therapy can be targeted to the tumor cells, patients have minimal exposure to the doxorubicin, and they therefore experience far fewer associated adverse events, such as cardiotoxicity, bone marrow suppression, and hair loss.

Postembolization syndrome is observed with bead embolization and is related to tumor ischemia and breakdown products from the tumor cells that are released into the bloodstream. Symptoms of postembolization syndrome typically include pain, fever, and short periods of hypotension; they are managed with supportive care. With advances in injection technique, most patients can be discharged home within 24 hours from the time of bead embolization.

Systemic Therapy

Systemic therapy is now considered the standard of care for patients with BCLC stage C tumors, and patients with stage A and B HCC are now increasingly treated with sorafenib. The label for sorafenib states that it is indicated for patients with unresectable HCC, and thus utilization continues to broaden. The risks and benefits of timing and incorporation of sorafenib therapy with resection or ablative techniques are not yet known. These questions are under investigation in 2 major clinical trials, the phase IV Sorafenib or Placebo in Combination with

Transarterial Chemoembolization for Intermediate-Stage HCC (SPACE)[20] and the phase IV Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of HCC (STORM) studies.[21] Both of these randomized trials are currently ongoing.

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Managing Adverse Events Associated With Sorafenib and Investigational Agents

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Sorafenib is an oral multikinase inhibitor that targets the Raf/Ras signaling pathway as well as the pathways stemming from the vascular endothelial growth factor (VEGF) and FMS-like tyrosine kinase 3.[1] The overall effect of sorafenib treatment is suppression of tumor cell proliferation and angiogenesis. Sorafenib received approval from the US Food and Drug Administration (FDA) for the treatment of unresectable HCC in 2007.[2] This approval was based in large part on the outcome of the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) study.[3] This phase III trial was a multicenter, double-blind, placebo-controlled study that randomized 602 patients with advanced HCC to treatment with either sorafenib or placebo. The study was halted at the second planned interim analysis, which showed a significant increase in median OS among patients in the sorafenib arm compared with the placebo arm (10.7 vs 7.9 months, hazard ratio, 0.69; 95% confidence interval, 0.55–0.87; $P<.001$). The median time to radiologic progression was nearly doubled among patients in the sorafenib group compared with placebo (5.5 vs 2.8 months; $P<.001$). There was no significant difference between the treatment arms regarding the other primary endpoint, median time to symptomatic progression (4.1 vs 4.9 months; $P=.77$).

In the SHARP trial, the overall incidence of serious adverse events was similar between the sorafenib arm and the placebo arm (52% vs 54%, respectively). A similar proportion of patients in each arm discontinued the study drug due to adverse events (38% vs 37%, respectively). A total of 26% of patients in the sorafenib arm required a dose reduction due to adverse events, and 44% required dose interruption (compared to 7% and 30%, respectively, in the placebo arm).

Hand-foot Skin Reactions

In the SHARP trial, one of the most common severe adverse events that occurred more frequently in the sorafenib group than in the placebo group was hand-foot skin reaction, or palmar-plantar erythrodysesthesia syndrome (8% vs <1%; $P<.001$); the overall (all grades) frequency was also significantly higher in the sorafenib arm (21% vs 3%; $P<.001$). The severity of hand-foot skin reaction is graded from 1–3, with grade 3 being the most severe.[4] Grade 1 is characterized by minimal skin changes or dermatitis without pain. Grade 2 is associated with more significant skin changes (such as peeling, blisters, bleeding, edema, or hyperkeratosis) and pain-limiting instrumental activities of daily living. Grade 3 is described as severe skin changes with pain that limits self-care activities. Hand-foot skin reactions are most effectively managed with the RAAR model: Remove, Avoid, Apply, and Report.[5] In this model, calluses and hyperkeratotic regions are removed with the aim of trying to heal the skin. Patients are advised to avoid factors that may aggravate the condition, such as sunlight, direct friction, hot water, constrictive footwear, and cleaning products containing strong chemicals. Application of moisturizers can provide a barrier of protection, and application of cold packs can provide short-term symptom relief.

Patients should be instructed to report signs of hand-foot skin reaction early, so as to avoid progression to more severe symptoms. Patient education should be emphasized, and patients should be informed that early intervention can reduce the need to discontinue sorafenib while symptoms resolve. The occurrence of hand-foot skin reaction may prompt a consultation with a podiatrist, who can remove any calluses and provide instruction about preventive methods, such as using protective padding, removing calluses, caring for fingernails and toenails, minimizing the risk of infection, wearing gloves or socks, and using emollients. A variety of different topical therapies may be recommended, including urea-based creams and topical analgesics. In addition, adjustments can be made with the sorafenib management approach according to progression of hand-foot skin symptoms.[5] For grade 1 symptoms, continuation of sorafenib is acceptable in conjunction with appropriate urea-containing topical medications and preventive measures. Grade 2 hand-foot skin reaction requires an immediate dose reduction of sorafenib without interruption of therapy, as well as the use of topical treatments and pain medications (including clobetasol, lidocaine, codeine, and pregabalin) in addition to those used for grade 1 skin reaction. Treatment of grade 3 hand-foot skin reaction begins with sorafenib interruption and treatment as described for grades 1 and 2 until improvement to grade 0 or 1. Sorafenib may then be reinitiated at a lower dosage, but it should be permanently discontinued if more than 2 grade 3 flares of hand-foot skin reaction occur. Overall, the most effective intervention for hand-foot skin reaction is active prevention, in order to prevent the devel-

opment of the syndrome into a serious advanced grade toxicity. Patients can be instructed to take digital images of bothersome skin irritations, which can then be electronically transmitted to a doctor or nurse for close follow-up and early evaluation, if the physician's office is geared to accept electronic medical information from patients. The key point is that using the above methodologic approach will ensure that most patients will receive a safe and adequate dose of sorafenib, considering the wide therapeutic index of the drug.

Diarrhea

In the SHARP trial, the other most common grade 3/4 adverse event that occurred at a higher frequency with sorafenib compared with placebo was diarrhea (8% vs 2%; *P*<.001). Diarrhea was also more frequent when considering all grades (39% vs 11%; *P*<.001). The effective management of diarrhea associated with sorafenib is dependent upon proper recognition of this adverse event; patients may have different definitions of diarrhea. Patients experiencing diarrhea should be advised to avoid foods that can exacerbate the condition, such as spicy or fatty foods. Additionally, antidiarrheal medications can be recommended to relieve symptoms. In the event of severe diarrhea, the dose of sorafenib should be adjusted; complete discontinuation of the drug is not necessary. Recommended dose reductions from the full dose of 400 mg twice daily are the same as for hand-foot syndrome: 400 mg daily, and then 400 mg every other day.

Fatigue

Fatigue is another major adverse event associated with sorafenib. Although its incidence in the sorafenib group was similar to placebo in the SHARP study (grade 3/4: 4% in each arm; all grades: 22% vs 16%), grade 3/4 fatigue occurred at a higher incidence (9.5%) in a previously conducted phase II clinical trial evaluating sorafenib in patients with advanced HCC.[6] Similar to diarrhea, the most important issue affecting the management of sorafenib-related fatigue is proper recognition. Many physicians do not immediately recognize patient fatigue, and it is therefore necessary to ask patients about whether they are able to perform their daily activities (even rudimentary personal activities such as bathing and dressing) and attend to their basic needs. Adjustments to the dose of sorafenib, similar to those described above, can be attempted in order to relieve fatigue.

Hypertension and Cardiac Events

The overall (all grades) incidence of hypertension was significantly higher among patients in the sorafenib arm compared with the placebo arm (5% vs 2%; *P*=.05) in the SHARP trial. The SHARP trial also reported a relatively higher frequency of cardiac ischemia and infarction with sorafenib (3% vs 1%). These findings were consistent with those recently reported in a study of 95 patients, which identified 44 cardiovascular events that occurred in 33 patients.[7] Of these events, hypertension accounted for the majority (62.2%); arterial ischemia and thrombosis were also reported. Because of the potential for cardiotoxicity with sorafenib, there is an important need to monitor phosphorous levels in patients receiving the agent. Hypophosphatemia, which occurred more frequently in the sorafenib arm, may lead to the development of cardiac dysfunction and may be an early indicator for this adverse event.

Novel Therapeutics in Development

The approval of sorafenib for the treatment of unresectable HCC, due to its ability to improve patient survival, revolutionized the systemic treatment of this disease. Based on the success of sorafenib in this setting, several agents have been introduced and are now currently under investigation for the treatment of HCC. In advanced clinical trials of these investigational agents, sorafenib treatment is used as the standard of care in the comparator arm.

The recombinant humanized monoclonal antibody bevacizumab, which inhibits the pro-angiogenic molecule VEGF, is currently approved for the treatment of a number of cancers, including those of the breast, lung, colon, and kidney, as well as malignant glioblastoma. A recent phase II clinical trial by Thomas and colleagues demonstrated that the combination of bevacizumab plus erlotinib resulted in favorable efficacy outcomes, including a median progression-free survival of 9.0 months, a median OS of 15.6 months, and a confirmed response in 25% of patients.[8] The promising results of this single-institution study are currently under investigation in a randomized phase II trial of bevacizumab plus erlotinib and sorafenib. Similar to sorafenib, the oral agent linifanib (ABT-869) is a multitargeted tyrosine kinase inhibitor with activity against both the VEGF receptor and platelet-derived growth factor receptor families. Recently, Toh and colleagues reported the results of an open-label, multicenter phase II trial of linifanib, which evaluated the agent in 44 patients with advanced HCC.[9] The proportion of patients who remained progression-free at 16 weeks was 31.8%; this rate was higher in patients with Child-Pugh A versus Child-Pugh B disease (34.2% vs 16.7%). Similarly, the median OS was 9.7 months; this rate was higher in patients with Child-Pugh A disease (10.4 vs 2.5 months). The most common grade 3/4 adverse events reported with linifanib were hypertension (18%) and fatigue (14%). Based on these successful results, linifanib is currently in phase III clinical development for HCC.[10]

Brivanib is a dual selective inhibitor of both the fibroblast growth factor receptor and the VEGF receptor.[11] Preclinical studies with brivanib suggested it inhibited tumor growth in an animal model of HCC.[12] This finding led to a phase II trial, the analysis of which was recently reported by Finn and colleagues.[13] In 101 patients with advanced HCC, brivanib induced both tumor responses and disease stabilization. Based on these promising data, brivanib is now being evaluated in a number of phase III clinical studies in the first-line and second-line settings.[14,15] Sunitinib is an orally available inhibitor of the VEGF and platelet-derived growth factor receptor as well as of c-Kit. Recently, a randomized phase III trial comparing the superiority of sunitinib against sorafenib was discontinued, following an independent review by the Data Monitoring Committee.[16] This review found that there was a higher incidence of serious adverse events in the sunitinib arm compared with the sorafenib arm, and it also showed that sunitinib did not meet the criteria to demonstrate either superiority or noninferiority in OS compared with sorafenib.

In a randomized, phase II clinical trial, sorafenib in combination with doxorubicin was evaluated against doxorubicin plus placebo.[17] The primary endpoint of median time to progression was 9 months for the doxorubicin plus sorafenib arm and 5 months for the doxorubicin plus placebo arm. An exploratory comparison of OS between the 2 arms showed a significant difference of 13.8 months in favor of doxorubicin plus sorafenib versus 6.5 months for doxorubicin plus placebo (P=.0129). Grade 3/4 toxicities included fatigue (15% in both arms) and neutropenia (55% with doxorubicin plus sorafenib vs 46% with doxorubicin plus placebo). Sorafenib-related toxicities included grade 3/4 diarrhea (11% in the sorafenib arm) and grade 3/4 hand-foot syndrome (9% in the sorafenib arm). The most concerning toxicity was an increased incidence of left ventricular dysfunction in the doxorubicin plus sorafenib arm (all grades: 19%; grade 3/4: 2%). These data suggest that a potential synergistic effect between doxorubicin and sorafenib leading to worsening cardiac function may exist. Anthracyclines such as doxorubicin depend on Ask-1 to exert their cell death effect. In liver cancer cells, a bFGF-mediated activation of Raf-1, one of the targets of sorafenib, may promote a complex between Raf-1 and Ask-1 at the mitochondrial level, leading to inhibition of Ask-1 kinase activity and prevention of stress-mediated apoptosis of anthracyclines. Inhibiting Raf kinase activity via sorafenib may release Ask-1 and restore the apoptotic activity of doxorubicin.[18] A large, randomized phase III intergroup trial (Cancer and Lymphoma Group B [CALGB] 80802), the first study guided by the National Cancer Institute for the evaluation of a systemic therapy in HCC, is currently recruiting patients with locally advanced or metastatic HCC to compare the combination of doxorubicin and sorafenib with sorafenib alone.[19]

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Multidisciplinary Treatment of Patients With HCC

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HCC is a disease that requires a multidisciplinary team approach to ensure appropriate management of patients, regardless of the stage of the disease. Options for HCC include curative surgical approaches, palliative locoregional treatments, and systemic therapies. Many of these options are employed through multidisciplinary clinics or teams comprised of surgeons, interventional radiologists, medical oncologists, and hepatologists, who work together to ensure the delivery of appropriate care for each patient diagnosed with HCC. This team works together to improve the patient's outcome and extend survival through coordinated management and application of the right therapy at the right time. Cases are often discussed at tumor board conferences, at which all members of the patient's management team evaluate the current plan and, when necessary, recommend other treatment approaches.

The majority of HCC cases are first screened by a hepatologist or gastroenterologist, mainly because these physicians care for patients with chronic liver disease. Because hepatologists and gastroenterologists play a primary role in caring for these patients, they should be aware that it is necessary to be diligent regarding HCC surveillance, and they should have a working knowledge of the available treatment modalities and should refer these patients to a multidisciplinary care team if HCC develops. The hepatologist and gastroenterologist also play an active role in managing the etiologic factors of HCC (eg, viral hepatitis) as well as cirrhosis.

Surgeons are key specialists in the management of HCC, although surgery may be curative in a limited number of patients. Interventional radiologists may help treat local advanced cases of HCC. The limitations of these approaches, however, should always be recognized once the disease progresses to more advanced stages that necessitate systemic therapy.

Medical oncologists are key specialists for advanced-stage HCC. The introduction of sorafenib and its use as the standard of care has enforced the role of oncologists in the treatment of HCC. Continued advancement of investigational agents will ensure the role of the medical oncologist in management of the HCC patient. Oncologists should be concerned not only with the administration of the anticancer medications, but also with the management of their associated toxicities; thus, their role in the multidisciplinary team is critical.

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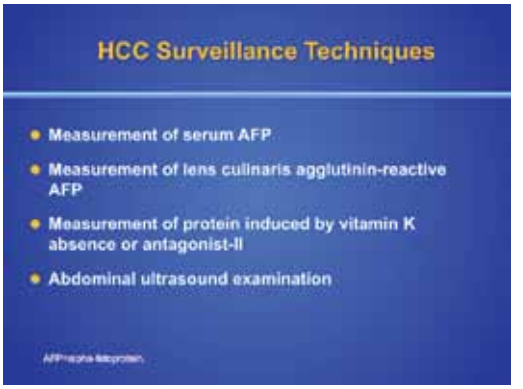

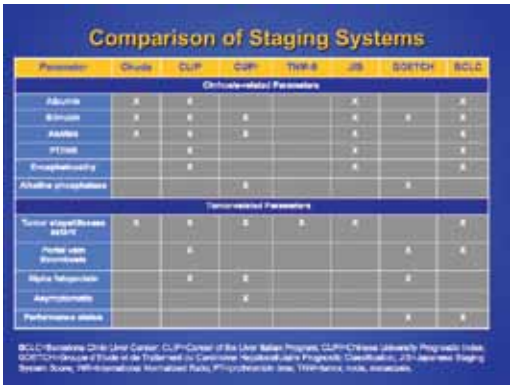

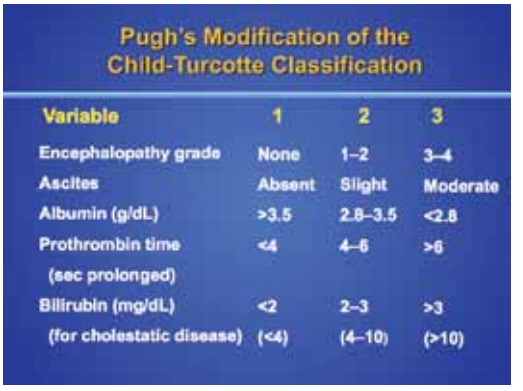

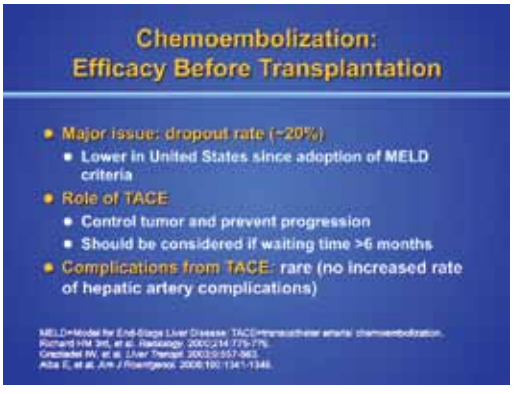

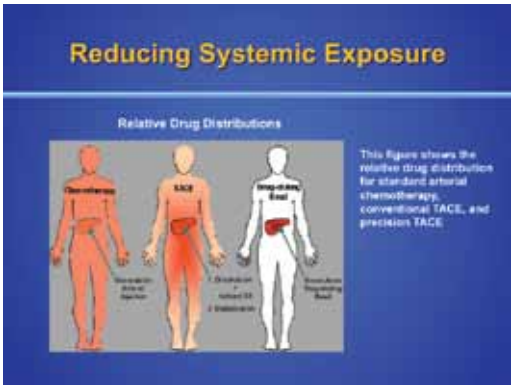

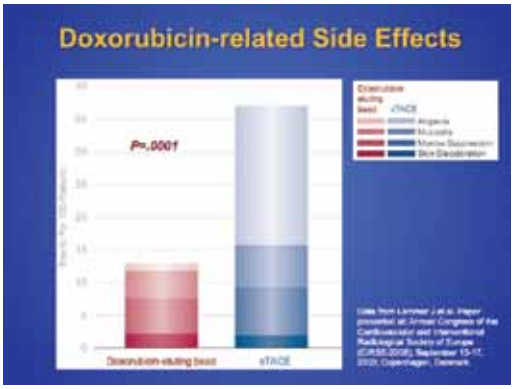

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