

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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## Emerging Agents for the Medical Therapy of Hepatocellular Carcinoma

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### **G&H** How do you stratify hepatocellular carcinoma patients to target the use of medical therapies?

**JL** Recently, the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) agreed on a common staging system, the Barcelona Clinic Liver Cancer (BCLC) Staging System, that divides hepatocellular carcinoma (HCC) patients into 4 stages. Patients at the early stage represent 30% of the US and European patient populations and are potential candidates for resection, transplantation, or local radiofrequency ablation as first-line therapy. Most are patients with well-preserved liver function and single nodal involvement.

Patients at the intermediate stage are defined by multinodular tumors without extrahepatic spread or vascular invasion and a lack of symptoms. These patients represent 15–20% of the HCC population in the United States and Europe, and are suitable candidates for chemoembolization. The rationale for this procedure in these patients lies in results of randomized controlled trials and meta-analysis of pooled data.

Patients at the advanced stage present with either vascular invasion or extrahepatic spread and cancer-related symptoms. These patients represent about 40% of the HCC population in the West. Until recently, there was no first-line treatment option for these patients. All the randomized controlled trials assessing systemic che-

motherapy, which have been conducted over the past 25–30 years, have had negative results. Therefore, the scientific societies have not recommended any first-line treatment options for advanced HCC and the US Food and Drug Administration (FDA) has not designated any drug indications for HCC treatment. This is a unique situation among solid tumors and represents a clear unmet need.

Finally, patients with end-stage disease represent 10% of the patient population. These patients present with very advanced disease with cancer symptoms and liver performance status in Child-Pugh class C, with very advanced hepatic dysfunction.

### **G&H** Is there a role for medical therapy in patients currently on the transplant waiting list, in order to prevent metastasization before a donor liver becomes available?

**JL** There are several studies, mostly phase II and case-control, assessing locoregional radiofrequency ablation and chemoembolization therapies in the waiting list population. Some of these studies suggest that therapy can provide benefit in the form of increased likelihood of successful transplant or overall survival improvement. However, there is no single randomized controlled trial of medical therapies in waiting list patients and thus no robust data endorsing any single strategy. This is one reason why none of the scientific societies or guidelines recommend a specific HCC treatment.

### **G&H** How have methods of percutaneous administration expanded the role of medical therapies in HCC?

**JL** There are two types of treatment that are administered percutaneously. Local radiofrequency ablation utilizes an ultrasound-guided probe to approach the liver through the skin and enter the tumor. The tumor is heated with steadily increasing temperature for approximately 15 minutes and literally burned. This method is efficacious in tumors of 2–3 cm in diameter or less, achieving complete response in 70–90% of cases. In 4-cm tumors, response is achieved in less than 50% of patients. Radiofrequency ablation is mostly indicated for single tumors or cases of 2 or 3 tumors, all less than 3 cm in diameter. There have been four randomized trials comparing radiofrequency ablation to a previously

utilized procedure, percutaneous ethanol injection. In ethanol injection, a needle is introduced into the tumor and delivers alcohol, which denaturizes proteins and kills the cells. Although it is not yet clear that radiofrequency ablation provides an advantage over ethanol injection in terms of overall survival, it has been shown to better control disease locally.

The other procedure currently in use is transarterial chemoembolization, which is reserved for patients with stage B or intermediate HCC. This procedure combines two types of treatment. A catheter is introduced into the hepatic artery through the femoral artery and guided to the tumor via angiographic imaging. This catheter is utilized to deliver a cytotoxic agent, either doxorubicin or cisplatin, with an emulsion of lipiodol that is retained within the tumor. Subsequently, microspheres are deployed to block blood flow to the tumor and create a secondary, ischemic insult that follows the cytotoxic assault. Seven randomized trials have been conducted comparing chemoembolization to no treatment and meta-analysis shows that chemoembolization improves survival in well-selected patients.

No distinct advantage has been noted with doxorubicin versus cisplatin and for the most part, the use of chemotherapy is not an area of active research. I know of no current plans for study of other chemotherapeutic agents in HCC chemoembolization.

#### **G&H** What other agents are under investigation for the treatment of HCC?

**JL** Over the last 10 years, new agents blocking signal transduction pathways central to proliferation and angiogenesis have been assessed in the management of all cancers. Several of these agents have been tested in HCC. Thus far, only one phase III trial has been conducted in HCC, assessing the tyrosine kinase inhibitor sorafenib (Nexavar, Bayer/Onyx). Several phase II trials have assessed various agents, including the tyrosine kinase inhibitors erlotinib (Tarceva, Genentech) and gefitinib (Iressa, AstraZeneca), which block epithelial growth factor receptors. The monoclonal antibody against epidermal growth factor receptor, cetuximab (Erbix, ImClone), has been examined as well.

We also have trials assessing multikinase inhibitors, including the anti-angiogenic agent sunitinib (Sutent, Pfizer) and a monoclonal antibody against vascular endothelial growth factor (VEGF), bevacizumab (Avastin, Genentech). Combination therapy of erlotinib with bevacizumab is also being investigated.

#### **G&H** Could you discuss research in treatment with sorafenib, including the latest phase III trial?

**JL** Sorafenib is a multikinase inhibitor that blocks the RAF component of the RAF/MEK/ERK signaling path-

way, as well as VEGF receptors. It acts in both tumor cells and endothelial cells. In preclinical cell line studies and experimental models, sorafenib decreased the proliferation of cells and increased apoptosis. In subsequent animal models, administration of sorafenib decreased the volume of tumors and extended survival. In 2005, a phase II study of sorafenib was reported in the *Journal of Clinical Oncology* that included 137 patients with end-stage HCC. The median survival time in this single-arm trial was 9.2 months, whereas the natural history of disease in patients at this stage affords a median survival of only 6–7 months.

Further, in advanced cases of HCC, our understanding of the molecular pathogenesis is such that we know there is activation of the RAF/MAP kinase pathway and activation of proangiogenic signals, mediated either by VEGF or angiopoietin-2. This knowledge, coupled with the phase II study results, made sorafenib an appealing agent for phase III research.

The recently completed phase III trial was a multinational, randomized, placebo-controlled trial conducted in 121 centers in 21 countries, mostly in Europe and the United States, but with additional investigators in South America, Australia, and New Zealand. The study included 602 patients who were randomized to sorafenib 400 mg twice daily versus placebo. The primary endpoint was overall survival and the secondary endpoint time to progression (TTP). Inclusion criteria allowed for rapid recruitment, and in 1 year 600 patients were inducted into the trial. There were two scheduled interim analyses. At the time of the second analysis, with data collected to October 17, 2006, the median survival in the active treatment arm was 10.7 months versus 7.9 months for placebo ( $P=.00058$ ). Median TTP were 5.5 and 2.8 months for sorafenib and placebo, respectively. With these results, the trial was stopped and all placebo patients were offered to cross over to sorafenib treatment.

Our group presented these data at the 2007 meeting of the American Society of Clinical Oncology (ASCO), and the complete study is being finalized for submission to a major peer-reviewed and indexed journal. These data represent the first successful use of a systemic drug to treat patients with advanced HCC and it is our hope that the results will allow for US FDA and European Agency for the Evaluation of Medical Products approval for treatment of HCC and endorsement by the scientific societies for first-line use. The next step in research will be to utilize sorafenib in the adjuvant setting after local ablation or resection in patients with early-stage disease. Currently, recurrence rates after resection or local ablation are 50% after 3 years, which is very high. Treatment with sorafenib may prove useful in lowering these rates.

#### **G&H** What is the current research status of the other targeted therapies under investigation for HCC?

**JL** In 2005, Philip and associates published their study of single-agent erlotinib therapy in 38 patients. They reported a median survival of 13 months but a TTP of only 2.2 months, which was not very consistent. Their study cohort included patients at both the intermediate stage (median expected survival of 16 months) and advanced stage of disease. The extended survival in these patients could be attributed to their heterogeneous nature or to the actual efficacy of the drug. Thus, erlotinib remains a good candidate for further research, given its targeted blocking of epidermal growth factor.

Bevacizumab, a monoclonal antibody against VEGF, was recently tested in 33 patients with advanced HCC in a study at Mt. Sinai Medical Center. One patient achieved complete response, and 3 or 4 patients achieved partial response. The median TTP was 6.5 months. However, several patients experienced complications. Gastrointestinal bleeding occurred in 2 patients, leading to death in 1 and vascular complications in the other.

The potent anti-angiogenic agent sunitinib was investigated in two phase II trials that were presented at this year's ASCO meeting. Each accrued about 50 patients with unresectable HCC. In one trial conducted at the Beaujon University Hospital in Clichy, France, there were 4 deaths as a result of treatment-related liver failure. These results lower our expectations for the utility of sunitinib, at least at full dose (50 mg/day). At 37.5 mg daily, as used in the other trial, there were no deaths related to liver failure, but there was 1 death related to gastrointestinal bleeding. The investigators reported 2 partial responses out of 50 patients.

### **G&H** Why has research of targeted therapy for HCC lagged behind that for other solid tumors?

**JL** There are several reasons for the delay in research. The first relates to the worldwide prevalence of HCC. Currently, after lung cancer and colon cancer, HCC is the third most common cause of cancer-related death, at 500,000 cases yearly. However, the incidence of HCC is much higher in East Asia, particularly areas of China and Japan, with 40 cases per every 100,000 individuals. In Northern Europe, incidence rates are only 10–15 per 100,000 individuals. In the United States, the prevalence is only 5 per 100,000 individuals. Lung, colon, breast, prostate, and other cancers occur as much as 5–10 times more often in Europe and the United States. Thus, pharmaceutical companies and researchers have prioritized these cancers for research and research funding.

Further, systemic chemotherapy and radiotherapy, the mainstays of oncologic treatment for the past 25 years, have never been effective for HCC. Therefore, physicians and industry researchers have not been optimistic about studying new compounds in this area.

Finally, HCC is, for the most part, managed by hepatologists and gastrointestinal physicians, with secondary care from surgeons, oncologists, radiologists, and pathologists. This is a unique situation. The majority of cancers, particularly advanced cancers, are managed by oncologists as the primary caregivers, which keeps industry and experts all in the same field. With HCC, hepatologists are the main caregivers and tend to have fewer ties to cancer-care-related pharmaceutical industry. In fact, two hepatologists (myself and Dr. Bruix) were the international primary investigators of the phase III sorafenib trial, which was highly unusual.

### **G&H** How has this delay affected current treatment options and research of molecular therapy for HCC?

**JL** In terms of FDA approval and use of molecular targeted therapies, there are 9 or 10 compounds approved thus far, and in a limited number of cancers: small-cell lung, breast, renal, head and neck, liver metastases, and pancreatic cancer (the last with somewhat controversial evidence). The evidence for approval in HCC is in place, so it is not so far behind the rest. And in general, the field is moving forward very quickly.

With these positive results with sorafenib, we are entering a new era in HCC treatment. As mentioned above, the next step is to test it in the adjuvant setting, in patients at earlier stages. Ultimately, given the complex molecular pathogenesis of HCC, I believe that future treatment will involve a combination of agents blocking multiple pathways.

### **Suggested Reading**

Llovet JM, Ricci S, Mazzaferro V, et al. Randomized phase III trial of sorafenib versus placebo in patients with advanced hepatocellular carcinoma (HCC). *J Clin Oncol*. 2007;25 (188 Pt. 1): 1s (abstract 1).

Faivre SJ, Raymond E, Douillard J, et al. Assessment of safety and drug-induced tumor necrosis with sunitinib in patients (pts) with unresectable hepatocellular carcinoma (HCC). *J Clin Oncol*. 2007;25 (188 Pt. 1): 149s (abstract 3546).

Zhu AX, Sahani DV, di Tomaso E, et al. A phase II study of sunitinib in patients with advanced hepatocellular carcinoma. *J Clin Oncol*. 2007;25 (188 Pt. 1): 231s (abstract 4637).

Philip PA, Mahoney MR, Allmer C, et al. Phase II study of erlotinib (OSI-774) in patients with advanced hepatocellular cancer. *J Clin Oncol*. 2005;23:6657-6663.

Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet*. 2003; 362:1907-1917.

Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology*. 2003; 37:429-442.

Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma: conclusions of the Barcelona- 2000 EASL conference. *J Hepatol*. 2001;35:421-430

Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis*. 1999;19:329-338.