

# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

## New Agents in Hepatocellular Carcinoma

Ghassan K. Abou-Alfa, MD  
 Medical Oncologist  
 Gastrointestinal Oncology Service  
 Department of Medicine  
 Memorial Sloan-Kettering Cancer Center  
 New York, NY

**H&O** What advances in the molecular understanding of hepatocellular carcinoma have led to improvements in therapy?

**GA-A** Classically, hepatocellular carcinoma (HCC) has been understood as a disease that is not responsive to chemotherapy as no therapy has shown an improvement in overall survival. With the advent of biologic therapies and the understanding of their different mechanisms of action, as well as the understanding of different pathways involved in the development of HCC, several concepts regarding possible therapies emerged. The most data in the setting of HCC exist for the multityrosine kinase inhibitor sorafenib (Nexavar, Bayer/Onyx).

**H&O** What have been the findings with sorafenib in HCC?

**GA-A** Sorafenib is a multikinase inhibitor. It inhibits Raf serine/threonine kinases, known to be overexpressed in HCC, vascular endothelial growth factor receptor, and platelet-derived growth factor receptor. An initial phase II trial assessing sorafenib in patients with advanced HCC did not meet its primary endpoint of tumor response. Treated patients, however, exhibited prolonged times of stable disease that were commensurate with an improvement in time to progression and median overall survival compared to historical controls. Along with the stable disease, “tumor necrosis” was noted—though this finding remains to be validated. This research was followed by a phase III double-blind randomized study of sorafenib versus placebo evaluating

median overall survival in patients with advanced HCC. This study demonstrated a clear improvement in median overall survival of patients who received sorafenib (10.7 months) versus placebo (7.9 months), which was clinically and statistically significant. The findings of this trial led to the approval of sorafenib by the US Food and Drug Administration (FDA) as the standard of care for patients with unresectable HCC.

**H&O** What have been the findings with other antiangiogenic agents in patients with HCC?

**GA-A** Sunitinib (Sutent, Pfizer) has been studied in two independent phase II studies in patients with advanced HCC. Both studies showed an improved outcome in their patient populations, with increased stability of disease and improved overall survival compared to historical controls. Bevacizumab (Avastin, Genentech) has been investigated as monotherapy, in combination with chemotherapy, and in combination with biologic therapies in patients with HCC. Improved outcomes were noted with bevacizumab, as in the sunitinib experience. Bevacizumab combined with erlotinib (Tarceva, Genentech/OSI) was found to be a promising combination in a phase II trial, with improved time to progression (9 months) and median overall survival of 19 months. Obviously, further studies are needed to better define the impact of sunitinib, bevacizumab, and the combination of bevacizumab and erlotinib in HCC.

**H&O** What is the role of combination therapy in patients with HCC?

**GA-A** My colleagues and I recently reported the results of the randomized phase II study of doxorubicin plus

sorafenib versus doxorubicin plus placebo in patients with advanced HCC. The combination of doxorubicin plus sorafenib showed improvements in time to progression (8.6 vs 4.8 months) and overall survival (13.8 vs 6.5 months). Proof of any synergistic role between sorafenib and doxorubicin would require a randomized phase III study of sorafenib plus doxorubicin versus sorafenib alone. It appears, though, that there is an important potential for combination therapy in HCC.

### **H&O** Are patients with early-stage HCC candidates for therapy with sorafenib?

**GA-A** For early-stage disease, the standard of care in HCC would typically be surgical removal of the tumor. For advanced-stage, local disease, embolization or chemoembolization is typically recommended. However, based on the available data, the FDA approved sorafenib for the treatment of unresectable HCC.

### **H&O** What new agents are under investigation in patients with HCC?

**GA-A** In the setting of metastatic HCC, IMC-A12, an insulin-like growth factor I receptor inhibitor, is currently under investigation both as monotherapy and in combination with sorafenib. In addition, there is a growing interest in adjuvant therapy for resected HCC. PI-88 (Progen), a heparan sulfate inhibitor, has shown promise in a randomized phase II study, with improved time to recurrence versus placebo. A new phase III double-blind randomized study evaluating PI-88 versus placebo in the adjuvant setting started to accrue patients recently.

### **H&O** What are the complexities of treating patients with varying degrees of hepatic dysfunction?

**GA-A** The safety and efficacy of sorafenib in patients with Child-Pugh B or C cirrhosis remains a subject of debate. In the phase II study evaluating sorafenib in 137 patients

with HCC, pharmacokinetic and drug-related toxicity profiles were comparable between the Child-Pugh A and B patients, although Child-Pugh B patients more often had worsening of their liver function. It remains unclear whether the total bilirubin elevation noted more often in Child-Pugh B patients is due to worsening liver function caused by sorafenib or simply due to an inhibitory effect of UGT1A1. It also remains unclear if the worsening liver cirrhosis was drug-related or associated with disease progression. Another study assessing the safety of sorafenib in patients with advanced liver dysfunction, by Miller and colleagues, found that a reduced dose of sorafenib is required with higher doses of bilirubin because of toxicity potentially manifested due to worsening of the bilirubin. A study that will attempt to answer the question whether sorafenib is safe to administer to Child-Pugh B and C cirrhosis patients will require a noninvasive way to evaluate any worsening in cirrhosis. Efforts in this regard are still under way.

### **Suggested Readings**

Abou-Alfa GK. Hepatocellular carcinoma: molecular biology and therapy. *Semin Oncol.* 2006;33(6 suppl 11):S79-S83.

Abou-Alfa GK, Schwartz L, Ricci S, et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol.* 2006;24:4293-4300.

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(18S): Abstract 3546.

Miller AA, Murry DJ, Owzar K, et al. Pharmacokinetic (PK) and phase I study of sorafenib (S) for solid tumors and hematologic malignancies in patients with hepatic or renal dysfunction (HD or RD): CALGB 60301. *J Clin Oncol.* 2007;25(18S): Abstract 3538.

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.

Thomas MB, O'Beirne JP, Furuse J, Chan AT, Abou-Alfa G, Johnson P. Systemic therapy for hepatocellular carcinoma: cytotoxic chemotherapy, targeted therapy and immunotherapy. *Ann Surg Oncol.* 2008;15:1008-1014.

Zhu AX, Abou-Alfa GK. Expanding the treatment options for hepatocellular carcinoma: combining transarterial chemoembolization with radiofrequency ablation. *JAMA.* 2008;299:1716-1718.

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(18S): Abstract 4637.