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Moving targets in hepatocellular carcinoma: Hepatic progenitor cells as novel targets for tyrosine kinase inhibitors

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Hepatocellular carcinoma (HCC) is the third leading cause of cancer death worldwide primarily because of endemic hepatitis B in Africa and Asia. It is also the most rapidly increasing cause of cancer death in the United States due to increased numbers of patients with chronic hepatitis C, and migration from endemic areas.¹

Since the majority of HCC patients present at an advanced stage, only about 20–30% receive potentially curative therapy such as resection or transplantation.^{2,3} Systemic treatments for advanced HCC have been disappointing historically. Underlying cirrhosis, found in about 80% of Western HCC patients, limits patient tolerance to many traditional anticancer agents. Furthermore, expression of P-glycoprotein pumps in HCC tumors leads to drug resistance. Most importantly, until recently, there has been a limited understanding of the pathogenesis underlying this disease.

Mechanisms of HCC pathogenesis are now beginning to be clarified.⁴ It is now known that several tumor suppressors or proto-oncogenes are mutated in HCC, including p53, Rb and IGF.⁴ In addition, many intracellular signaling pathways have now been shown to contribute to HCC growth. Clinically, among the most important are those related to vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and their downstream signaling cascades.⁵

At the 2007 American Society of Clinical Oncology meeting, sorafenib, an oral multikinase inhibitor of raf kinase, VEGFR2, VEGFR3 and PDGFR- β kinases, was reported to lead to an improvement in overall survival by about 3 months when compared with placebo in a large, randomized trial of advanced HCC patients.⁶ Other drugs targeting molecular pathways in HCC also show promise, including other tyrosine kinase inhibitors, such as erlotinib (a tyrosine kinase inhibitor against EGFR),⁷ and more “promiscuous” kinase inhibitors such as sunitinib (which targets VEGFR, c-kit, and the platelet-derived growth factor receptor, PDGFR).⁸ In addition to tyrosine kinase inhibitors, drugs targeting the ligands for some of these receptors also show activity against HCC, particularly bevacizumab, a monoclonal antibody against VEGF.⁹

Imatinib mesylate is also an inhibitor of several tyrosine kinases, including PDGFR, c-kit, and the bcr-abl fusion product. This drug has proven efficacy against diseases which involve each of these molecular targets, most notably chronic myelogenous leukemia (CML) which involves a constitutively active tyrosine kinase caused by the bcr-abl translocation.¹⁰ Up to 25% of

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HCCs are reported to express c-kit,^{11,12} suggesting the possible utility of studying imatinib in HCC.

In addition to direct targeting of tumor-related growth pathways, other paradigms for treating cancer have emerged using tyrosine kinase inhibitors. One of these includes targeting the tumor “stroma,” including endothelial cells and fibroblasts which support cancer cell growth. For instance, Bergers and colleagues showed that by targeting PDGFR, they could dysregulate peri-endothelial cells in a mouse model of islet cell cancer. This mechanism complemented direct targeting of VEGF receptors on endothelial cells by a different tyrosine kinase inhibitor.¹³ Similarly, in the liver, hepatic fibroblasts and endothelial cells may contribute to carcinogenesis. Animal models of HCC have revealed that targeting endothelial cell proliferation can lead to a reduction in activated cancer growth pathways.¹⁴ Thus, targeting the “soil” as well as the tumorigenic “seeds” may provide additional treatment benefits against HCC and other cancers.

Now, Knight and colleagues in this issue of *Gastroenterology* suggest another possible mechanism of antitumor activity using imatinib for HCC by targeting presumptive hepatic progenitor cells.¹⁵ Hepatic regeneration from chronic liver injury involves recruitment of progenitor cells from the adult liver’s stem cell compartment. These progenitor cells, some of which are c-kit positive, may also be associated with carcinogenesis.¹⁶ This has led to the theory that HCC may arise in part from maturation arrest of these progenitor cells.¹⁷ Thus, targeting this population of cells using imatinib or other drugs may inhibit tumorigenesis.

The authors evaluated different types of liver inflammation by studying mice receiving a choline-deficient diet, and human liver tissue from subjects with chronic hepatitis B. They found upregulation of PDGF-C and c-kit expression in the choline-deficient animal model, and c-kit positive progenitor cells were observed adjacent to hepatocytes in all the human sections. The number of c-kit positive cells in the human specimens also correlated with disease severity. Use of imatinib led to decreased proliferation of liver progenitor cells in culture, and reduced numbers of liver progenitor cells and liver tumors in the choline-deficient mice.

In an earlier publication, the same authors noted similar antiproliferative effects of alpha interferon on hepatic progenitor cells in pre- and post- treatment liver biopsies in patients with hepatitis C. They found a 50% decrease in the numbers of c-kit positive hepatic progenitor cells in humans treated with interferon. In choline-deficient mice, they found a four-fold reduction in the number of oval progenitor cells.¹⁶ In clinical support of these data, interferon has been demonstrated to decrease the subsequent risk of HCC in cirrhotics with HCV, and numbers of hepatic progenitor cells may be lower in those who have responded to interferon therapy.¹⁸

Unfortunately, two phase II human trials using imatinib in advanced HCC have been disappointing, with no objective responses observed in those with established HCC.^{19,20} It is possible that imatinib or similar drugs may play a more active role in HCC chemoprevention by targeting liver progenitor cells that are upregulated in the context of inflammation. Imatinib may be more effective when also used in combination with anti-VEGF treatment or other therapies.

Many other questions remain. The authors show that some liver progenitor cells are c-kit positive, and that these cells have some carcinogenic properties. However, there is no consensus about which specific markers best define hepatic progenitor cells or HCC stem cells, and whether c-kit is the most promising target for therapy. The phenotype of HCC cancer stem cells is currently under active investigation. Initial studies suggested that CD133 (+) cells might define tumorigenic progenitors in HCC,²¹ but Yang and colleagues subsequently showed that

CD 90 (+) and CD 45 (–) cells may be more sensitive markers of hepatic cancer stem cells.^{22,23}

It is also unknown whether one cell target will ultimately be adequate to destroy the reservoir of progenitor cells, or whether complete eradication of these cells is necessary for effective prevention and/or treatment of HCC in humans. Furthermore, as Knight and colleagues point out, the adverse effects of targeted therapies in these settings is unclear. In particular, imatinib can cause fluid retention and hepatic toxicity, both of which may make it particularly difficult to use in patients with established cirrhosis, especially in the context of chemoprevention.

Liver tumors with progenitor cell characteristics may be particularly aggressive clinically. Lee and colleagues have shown that patients with HCCs with a gene expression profile similar to hepatic progenitor cells had a worse prognosis than those without this pattern.²⁴ Similar to the situation in HER-2 positive breast cancer, markers for tumor aggressiveness may ultimately yield novel prevention and/or treatment opportunities.²⁵ While much remains to be learned, targeting hepatic progenitor cells in HCC is a novel treatment paradigm as presented in this issue which will complement the development of therapeutics directed against tumor and stromal cells. Hopefully this will lead to improved outcomes for our patients in the future.

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