Antiangiogenic Therapy for Advanced Hepatocellular Carcinoma

Worldwide, primary liver cancer is the sixth most common malignancy and the second most common cause of cancer-related death. In the US, an estimated 19,169 new cases of liver and intrahepatic bile duct cancer are expected in 2017, with 7,680 deaths from the disease. Hepatitis C virus (HCV)–related hepatocellular carcinoma, and non-alcoholic steatohepatitis associated with diabetes and morbid obesity. Hepatitis C virus (HCV) – believed to infect 4 million Americans – is associated with 25% of liver cancer cases.

HCC tends to be particularly vascular and, like all solid tumors, requires angiogenesis to grow beyond a few millimeters in size. Angiogenesis is evident in early stage liver carcinoma and correlates with disease progression9. The primary stimulus for angiogenesis is the release of vascular endothelial growth factor (VEGF), an endogenous cytokine that induces capillary endothelial cell proliferation, migration and survival, and the induction of bone marrow–derived endothelial cells (EPCs) to form the new vasculature.

VEGF is overexpressed in most solid tumors and may be further upregulated by external stimuli. In various in vitro tumor models, chronic alcohol exposure, a known risk factor for HCC and other cancers, has correlated with increased VEGF expression, tumor growth and tumor vessel density, suggesting that promotion of angiogenesis may be one possible mechanism of alcohol-induced tumor progression. Other angiogenic factors, such as platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF), are also expressed in HCC.

Clinical Efficacy of Antiangiogenic Therapies for HCC

The inherent vascularity of HCC makes it a logical target for antiangiogenic therapies. Sorafenib (Sutent), a small molecule tyrosine kinase inhibitor (TKI) that binds competitively to the intracellular receptor domains for VEGF, PDGF, and other angiogenic growth factors, led to an overall survival (OS) benefit in advanced HCC that was confirmed and expanded in the SHARP trial2. Sorafenib induces a ~3 month survival benefit over placebo in 602 patients with unresectable HCC who had not received prior treatment. Median OS was 10.7 mos. (HR=0.71; P<0.000058). In a phase 2 trial of sunitinib in advanced HCC, 56 patients received sunitinib 15 mg/day as the first-line treatment for advanced HCC, and 13 of those patients went on to achieve liver-only progression-free survival (PFS) of 7 months. Median OS was 17 mos. (HR=0.50; P=0.000007; HR=0.58).

While the 2 (23%) of sorafenib-treated patients in SHARP achieved a partial response (PR), 71% had stable disease (SD). In the phase 2 sorafenib study, HCC-related deaths were the most frequent cause of death in sorafenib-treated patients, which occurred despite an increase in tumor size10. This finding may help explain why a survival benefit is observed with sorafenib, in the absence of evident tumor regression, although this hypothesis requires validation. It should also be noted that most patients in SHARP (95%) had Child-Pugh A and good performance status, and only 40% who received sorafenib had underlying viral hepatitis. Future clinical studies will therefore need to evaluate the safety and efficacy of sorafenib in patients with more severe cirrhosis and worse liver function usually seen by medical oncologists.

Most recently, final outcome data were presented from a randomized phase 2 study of bevacizumab and gemcitabine/doxorubicinplusepsilonepsilonepsiloplatel- derived endothelial progenitor cells (EPCs) to the new vasculature. Metronomic Chemotherapy

Cancer chemotherapypart 3: of VEGF by host stroma proximal to the tumor, activation of alternative signaling pathways, co-option of existing vessels, and recruitment of resident tumor vasculature to a more mature, less VEGF dependent phenotypede4, 14.

There are considerable data supporting the targeting both the VEGF and EGF pathways simultaneously as a means to circumvent anti-VEGF escape15. For example, some preclinical evidence suggests that inhibiting VEGF may make tumors more angiogenesis dependent, and therefore more susceptible to VEGF inhibition16. As previously discussed, encouraging results were observed in a phase 2 study of bevacizumab in advanced HCC, and this combination is being evaluated further in HCC and other tumor types.

Side Effects of Antiangiogenic Therapy in HCC

The risk for bleeding, a concern in any HCC patient, is elevated in those undergoing treatment with a VEGF inhibitor. Six patients in the placebo arm developed intraperitoneal hemorrhage, and 1 patient had grade 3 hematuria/azotemia in the phase 2 study of single-agent BV for advanced HCC. Hypertension is also a well-documented side effect of VEGF inhibition and was observed in 40% of patients treated with sunitinib. One frequent adverse event associated with sorafenib in the SHARP trial was fatigue, diarrea, weight loss, rash/desquamation, hypothyroidism due to varicella zoster skin reaction, alopecia, anorexia, nausea and abdominal pain17. Although grade 3/4 bleeding in SHARP was very rare, clinicians should be aware of the potential for increased bleeding risk with sorafenib. Sunitinib was associated with grade 3/thrombocytopenia, neutropenia, anemia, asthma, and azotemia in a phase 2 HCC study. Four patients had grade 5 bleeding, dropping, dizziness, gastrointestinal and renal failure attributed to sunitinib therapy.

Future Directions

Antiangiogenic therapies appear poised to markedly alter the treatment outlook for patients with advanced HCC. Combination therapies, new therapeutic targets, better patient selection based on tumor characteristics, and the adoption of imaging techniques that measure tumor perfusion are almost certain to provide further advances. Furthermore, pilot studies are underway to examine the potential role of anti-VEGF therapy in adjuvant HCC treatment settings, post-resection, and post-chemoembolization for inoperable HCC.

From the Editor-in-Chief

The Angiogenesis Foundation is pleased to present this targeted and focused issue on Targeting Tumor Angiogenesis for advanced hepatocellular carcinoma. I have invited three preeminent experts, Drs. Ghassan K. Abou-Alfa, Melanie Thomas, and Alan Venook, to discuss the latest evidence in the treatment of advanced HCC and what the future holds for new therapeutic targets under investigation.

William L. Wi, M.D., President, The Angiogenesis Foundation

References


www.angio.org

For complete references, please see www.angio.org and click on CME Information.
Targeting Cells and Pathways in Liver Cancer
During tumor angiogenesis, endothelial cells recruit pericytes to stabilize blood vessels perfusing tumors. Endothelial cells also provide paracrine factors to tumor cells which, in turn, release growth factors that sustain angiogenesis. Key pathways in each cell can be targeted for therapy.

Targeted Agents
(Targeted shown in diagram above and to the right)
- Bevacizumab (Avastin)
- Sorafenib (Nexavar)
- PI-88

Targeting Tumor Angiogenesis
1. Recipient cancers lack a blood supply and cannot grow larger than 2-5 mm in size.
2. Cancer cells release growth factors that activate endothelial cells during the switch from the anergic phenotype, which occurs in response to gene mutations and hypoxia.
3. Angiogenic vessels form tubes and loops, thereby delivering oxygen, nutrients, and survival factors to cancer cells.
4. Vessels mature as pericytes are recruited by endothelial cells to stabilize new capillaries.
5. Unabated angiogenesis enables tumor expansion and local invasion. Abnormal blood flow leads to collateral hypoxia. Vessel hyperpermeability results in tumor edema.

How blood vessels spread (growth factors bind to endothelial cell receptors, activating signal transduction pathways and causing cell proliferation. Sprouting vessels secrete matrix metalloproteinases (MMPs) and secrete matrix metalloproteinases (MMPs) and migrate towards the tumor using specific cell integrins.)

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