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Targeted Therapy for Hepatocellular Carcinoma

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Hepatocellular cancer (HCC) is a leading cause of cancer death worldwide, and most patients who are diagnosed with HCC are ineligible for curative local therapy. The targeted agent sorafenib provides modest survival benefits in the setting of advanced disease. Novel systemic treatment options for HCC are sorely needed. In this review, we identify and categorize the drugs and targets that are in various phases of testing for use against HCC. We also focus on the potential for combining these agents with radiotherapy. This would help identify directions for future study that are likely to yield positive findings and improve outcomes for patients with HCC.

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Hepatocellular cancer (HCC) is a leading cause of cancer death worldwide, particularly in developing countries.[1] HCC incidence rates are increasing in many parts of the world, including the United States.[2] Most of the patients diagnosed with HCC are not eligible for radical curative therapy, and median survival for such patients is less than 1 year.[3] At present, there are few effective treatments available for patients with unresectable HCC.

Transarterial chemoembolization has been found to provide a survival benefit for patients with unresectable HCC.[4] Most systemic treatments such as cytotoxic chemotherapy and hormonal therapy do not improve overall survival.[5] Alternative therapeutic approaches for patients with advanced HCC are consequently being explored.

Ionizing radiotherapy (RT), which plays a major role in the management of most solid tumors, is not commonly used to treat HCC. RT has historically yielded suboptimal results in the treatment of HCC with regard to both treatment efficacy and toxicity.[6-8] With the advent of stereotactic body RT (SBRT), RT has emerged as a promising option for selected cases of localized HCC.[9,10]

In the European Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol Trial, the multitargeted small molecule tyrosine kinase inhibitor sorafenib improved median survival over placebo for inoperable HCC patients with Child-Pugh A cirrhosis from 7.9-10.7 months.[11] A randomized trial conducted in Asia also demonstrated that sorafenib confers a survival benefit in this setting.[12] These studies established sorafenib monotherapy as the standard first-line systemic treatment for advanced HCC around the world.[13]

Sorafenib is one of many targeted agents used by oncologists today. Advances in cancer biology have elucidated numerous cellular signaling mechanisms that are critical to tumor development, progression, and metastasis. Inhibitors of these pathways are constantly being developed and tested as potential anticancer agents in preclinical and clinical studies. Signaling cascades that are thought to be critical in HCC formation and progression include the MAPK/ERK pathway, the PI3Kinase/AKT/mTOR pathway, the Wnt/β-Catenin pathway, and angiogenic pathways.[14]

Asides from sorafenib, no targeted agent is currently approved for the treatment of HCC. In this review, we identify and categorize the drugs and targets that are in various phases of testing for use against HCC. We also comment on how some of these agents may act synergistically with ionizing RT. This would help identify directions for future study that are likely to yield positive findings and improve outcomes for patients with HCC.

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Angiogenesis

Angiogenesis has long been recognized as an important component in the growth of many solid tumors,[15] including HCC.[16] Antiangiogenic drugs, such as bevacizumab and thalidomide, are used in the treatment of numerous malignancies. Increased levels of the proangiogenic factor vascular endothelial growth factor (VEGF) in HCC tissue or patient serum are associated with inferior clinical outcomes.[17] Dozens of agents being studied in clinical trials for HCC act, at least in part, by inhibiting angiogenesis. Several specific molecular targets for antiangiogenic agents are being explored.

Angiogenesis: VEGF and PDGF

The only approved targeted agent for HCC, sorafenib, exerts antiangiogenic effects through VEGF receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) inhibition. Numerous other agents that are being tested in clinical HCC trials target VEGF (eg, bevacizumab and cabozantinib), platelet-derived growth factor (PDGF) (eg, MEDI-575 and preretinoin), or both VEGF and PDGF (eg, axitinib and nintedanib). Ramucirumab, which targets VEGFR2 and is approved for the treatment of advanced gastric cancer, failed to improve overall survival compared with placebo in a large randomized trial.[18] Interestingly, a survival benefit was observed in patients with alpha-fetoprotein exceeding 400 ng/mL. On the other hand, a large randomized study comparing sunitinib, which targets both VEGF and PDGF, to sorafenib was discontinued because of increased serious adverse events and inferior efficacy in the experimental sunitinib arm compared with the control sorafenib arm.[19] Brivanib, which inhibits VEGFR and fibroblast growth factor (FGF) receptor, was been given orphan drug status by the European Union based on promising phase II data. In a large randomized trial comparing brivanib with sorafenib, brivanib demonstrated comparable antitumor efficacy but was less well-tolerated than sorafenib.[20] Other ongoing HCC trials are examining the combination of anti-VEGF or PDGF agents such as sorafenib with other treatments, including cytotoxic chemotherapy, other targeted agents, and radiation therapy. However, a recent large cooperative group trial was reported at ASCO 2016 that showed no benefit to adding doxorubicin to sorafenib.

Among the agents mentioned above, sorafenib has been subject to the most study as a radiosensitizer. Preclinical data demonstrate that sorafenib can synergize with RT in HCC models through several mechanisms.[21,22] Early-phase clinical trials demonstrate that this combination has significant activity but also may be associated with high rates of liver toxicity.[23,24] Preclinical studies also support the sequential use of sorafenib and RT.[25] This strategy is being studied in an ongoing phase III trial (NCT01910909).

Angiogenesis: Other Angiogenic Targets

Antiangiogenic drugs that work via mechanisms other than VEGFR and PDGFR inhibition are also being developed. We believe that these agents are particularly promising for the treatment of HCC. Of note, these agents have received little attention as potential radiosensitizers in preclinical and clinical trials.

The angiopoietin-Tie system plays a key role in remodeling and maturation of blood vessels[26] as well as lymphatic vessels.[27] The angiopoietin family includes 4 ligands (Ang-1, Ang-2, Ang-3, and Ang-4) and 2 corresponding tyrosine kinase receptors (Tie1 and Tie2). Ang-1 and Ang-2 have antagonistic effects, and increased Ang-2 expression has been found in HCC lesions compared with surrounding liver tissue.[28] In surgical series, Ang-2 expression and high Ang-2/Ang-1 ratios have been linked to higher tumor grade, increased microvessel density, and inferior clinical outcomes.[28-30] In a correlative study performed on patients enrolled on the study of heart and renal protection trial, the angiogenesis biomarkers Ang-2 and VEGF were independent predictors of survival.[31]

Several agents that target the angiopoietin or Tie system are being studied in HCC trials. Regorafenib (fluoro-sorafenib, BAY73-4506) is an oral multikinase inhibitor that potently inhibits Tie2 as well as VEGFR2, VEGFR3, PDGFR-beta, c-kit, Flt-3, and Raf kinases. Regorafenib is currently being tested as second-line treatment for HCC in a large randomized trial.[32] AMG-386 is an antiangiopoietin peptibody that inhibits the interaction between the ligands ang-1 and ang-2 with the Tie-2 receptor.[33] There are several clinical trials testing AMG-386 for the treatment of HCC, some of which use a combination of AMG-386 with sorafenib.

Heparan sulfate (HS) mimetics are an intriguing class of antiangiogenic molecules. They work by inhibiting heparanase, which cleaves HS and participates in remodeling the extracellular matrix and is preferentially expressed in human tumors.[34,35] Antiangiogenic effects are thought to be mediated via antagonism of the interactions of angiogenic growth factors and their receptors with HS.[34] The HS mimetic PI-88 is being studied for a number of malignancies and has reached phase III testing as adjuvant therapy for resected HCC based on encouraging phase II results.[36,37]

c-Kit

c-Kit, also known as mast or stem cell growth factor receptor and CD117, is a protein encoded by the KIT gene.[38] c-Kit signaling plays a role in cell survival, proliferation, and differentiation. Many agents that act upon c-Kit also target the VEGF and PDGF pathways. An exception is dasatanib, which targets BCR/ABL, Src, c-Kit, ephrin receptors, and several other tyrosine kinases and is approved for second-line use in chronic myelogenous leukemia and for Philadelphia chromosome-positive acute lymphoblastic leukemia. Accrual to a Phase II trial of dasatinib for unresectable HCC has been completed, and results are pending. A phase II study testing imatinib, which also inhibits BCR/ABL and c-Kit, yielded discouraging results.[39] Although preclinical studies indicate that imatinib may have radiosensitizing properties in a variety of tumor models,[40-43] this combination has not been studied extensively in preclinical or clinical trials for HCC.