Combining Antiangiogenesis Treatment and Chemoembolization

A new approach for managing hepatocellular carcinoma.

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Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death behind only lung and colon cancers.[1] Eighty percent of new cases occur in developing countries, but the incidence is increasing in economically developed regions, including the United States.[1] Importantly, in the Western Hemisphere, only 30% of patients are diagnosed at an early stage and are eligible for curative therapies, such as resection or transplantation. For patients diagnosed with unresectable HCC, several nonsurgical palliative treatment options exist, including transcatheter arterial chemoembolization (TACE).[2] TACE exploits the preferential blood supply of liver tumors from the hepatic artery for targeted delivery of chemotherapeutic agents and embolization particles to the tumor vascular bed, while sparing the surrounding liver parenchyma.[3] TACE has been shown to have a survival benefit for patients with intermediate and advanced stages of HCC.[2,4,5]

The fundamental role of angiogenesis in tumor progression was first suggested by Hlatky et al in a classic study describing that tumors cannot grow beyond 1 or 2 mm without the formation of new blood vessels.[6] This complex process facilitates tumor progression and eventually tumor metastatic spread.[6,7] Several factors, including tumor hypoxia, growth factors, cytokines, oncogene activation, and other mutations interact to stimulate angiogenesis.[7,8] Therefore, targeted inhibition of angiogenesis can be achieved at any of these levels with various treatments designed to bind growth factors with monoclonal antibodies, inhibit the downstream signaling from tyrosine kinase receptors, or disrupt the interaction between proliferating endothelial cells and matrix components.

Theoretically, after antiangiogenic treatment, the tumor vasculature may undergo morphologic changes, whereby immature blood vessels are pruned, blood vessel tortuosity and dilation decrease, and a closer association between per-icytes and endothelial cells is induced.[9] As a result, tumor blood vessel leakage, vascular permeability, and interstitial fluid pressure decrease. If chemotherapy is administered after antiangiogenic drug-induced vascular changes, it can be quite advantageous because it would result in increased intratumoral drug delivery as well as an increase in the number of tumor cells that are sensitive to chemotherapy. A recent study showed that there is improved penetration of the chemotherapy into the tumor upon vessel normalization.[10]

Until recently, there was no standard systemic therapy for unresectable HCC. The introduction of antiangiogenic therapy, such as the multikinase inhibitor sorafenib, has changed the management algorithm of patients with advanced disease.[11,12] Because antiangiogenic drugs are generally cytostatic rather than cytotoxic, combinations involving conventional cytotoxic chemotherapies with antiangiogenesis drugs may be useful for maximizing therapeutic efficacy. Moreover, given that HCC presents as hypervascular tumor(s), combining therapies that inhibit angiogenesis on a molecular and mechanistic level seems particularly attractive. Finally, given the fact that TACE directly causes angiogenesis through activation of the hypoxia-mediated pathway (hypoxic changes in the tumor directly upregulate angiogenesis via vascular endothelial growth factor [VEGF]) thereby potentially limiting its efficacy, it was logical to combine TACE with agents that directly counteract this angiogenic activity.

The administration of antiangiogenic therapy in conjunction with locally delivered chemotherapy can help improve penetration of the chemotherapy into the tumor upon vessel normalization.[10] In this article, we briefly report on preliminary studies that combine antiangiogenic therapy administered systemically with transcatheter intra-arterial chemoembolization.
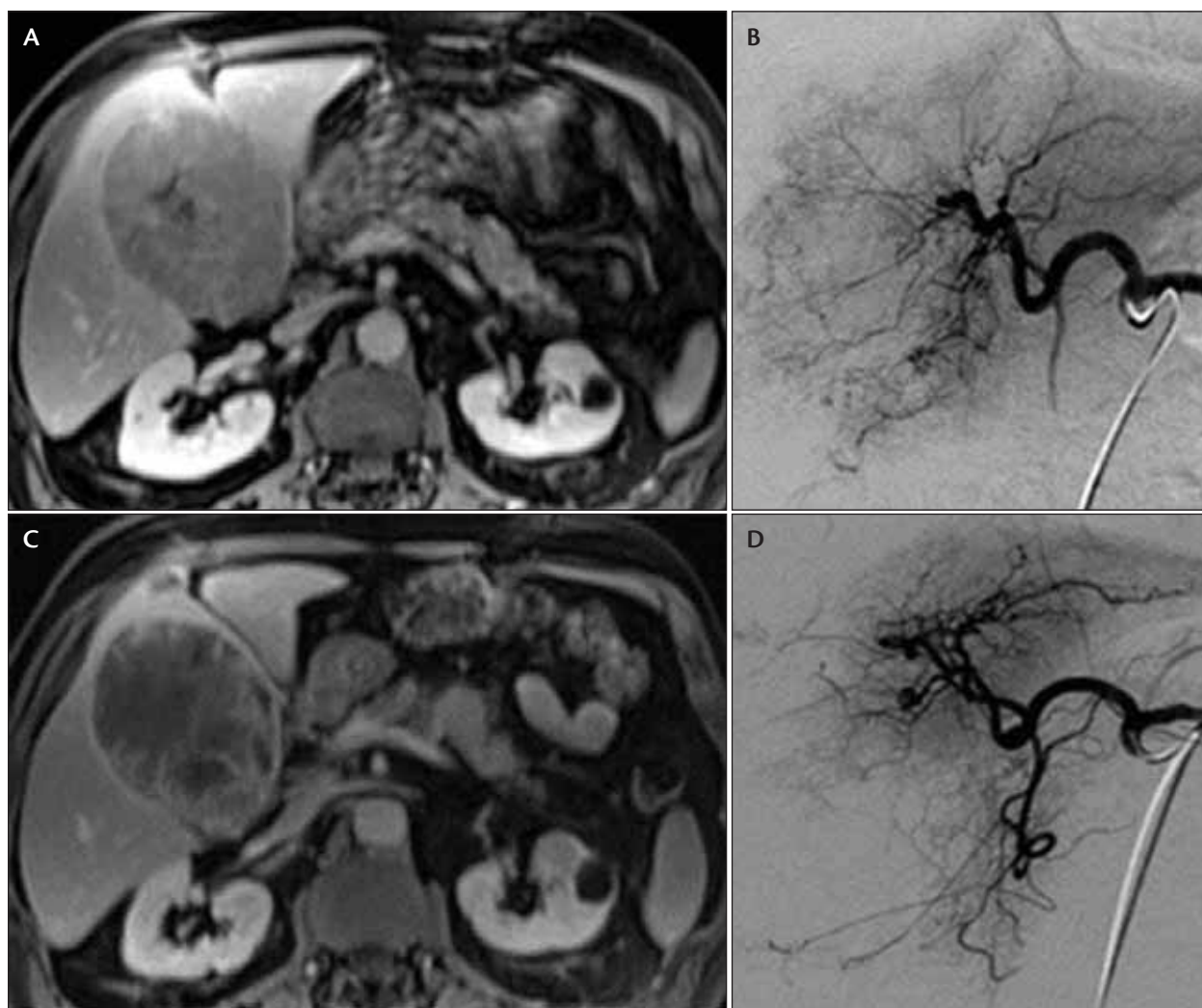
Figure 1. Significant increase in the amount of tumor necrosis and decreased tumor vascularization in a 68-year-old patient who received sorafenib followed by two cycles of TACE. The patient was bridged to surgical resection 3 months after the second cycle of TACE. Axial magnetic resonance imaging (MRI) of the liver showing a 10.3-cm hypervascular HCC, located in the right hepatic lobe, with 90% enhancement (A). Selective digital subtraction angiogram of the tumor, during the first TACE procedure, demonstrating increased hypervascularity (B). Axial MRI of the liver, 3 weeks after baseline MRI (A) demonstrating now, a similarly sized tumor but with increased tumor necrosis and 30% enhancement (C). Selective digital subtraction angiogram of the tumor during the second cycle of TACE, showing minimal contrast uptake of the necrotic portion of the tumor (D).

BEVACIZUMAB AND TACE

One of the most critical and specific factors for blood vessel formation is VEGF.[13] VEGF is an endothelial cell mitogen that regulates proliferation, permeability, and survival of endothelial cells through inhibition of apoptosis.[13-15] HCC is one of the most vascular solid cancers associated with a high propensity for vascular invasion and a high expression of VEGF.[4,16,17] Upregulation of VEGF has been correlated with increased tumor invasion, intratumoral microvessel density, disease recurrence, and poor prognosis.[18-20] One approach to inhibit angiogenesis is to use monoclonal antibodies directed at VEGF.[21,22]

Bevacizumab is such a humanized monoclonal antibody that, through binding to VEGF, it prevents the interaction of VEGF with its receptors on the surface of endothelial cells. When unblocked, this interaction may lead to endothelial cell proliferation and new blood vessel formation.[23] VEGF expression is known to play an important role in the development of HCC, and the degree of its expression is reported to be associated with tumor size and histologic grade. Several studies have explored the potential therapeutic role for bevacizumab in patients with HCC.

The results of the first United States phase II study combining antiangiogenic therapy with TACE were

recently presented.[24] Tumor response and safety of concurrent bevacizumab and TACE were evaluated in 26 patients with unresectable HCC (Eastern Cooperative Oncology Group status, 0–2; Child-Pugh stages, A–B; Barcelona Clinic Liver Cancer classes, B–C). These patients received bevacizumab 10 mg/kg every 2 weeks, in addition to TACE, in a 6-week cycle (on average, 1–3 cycles). The primary endpoint was tumor response, assessed by MRI at baseline and 3 weeks after TACE, using size (Response Evaluation Criteria In Solid Tumors [RECIST] criteria) and contrast-enhancement (European Association for the Study of the Liver [EASL] criteria). Secondary endpoints included safety and survival.

On follow-up imaging, index lesions had a mean decrease in size of 13% ($P < .0005$). Using RECIST, eight (35%) patients achieved partial response, and 15 (65%) patients had stable disease. Targeted tumors showed a mean decrease in contrast enhancement of 69% ($P < .0005$). By EASL criteria, 14 (60%) patients had complete or partial response, and nine (39%) had stable disease. The disease control rate was 100% using either criteria while undergoing treatment. Median overall survival was 13.5 months, with 10 patients still alive. Fifteen (58%) patients experienced grade 3/4 toxicities possibly related to either therapy, with most toxicities resolving within 2 months of therapy. Overall, the combination therapy of bevacizumab and TACE was reasonably well tolerated in unresectable HCC patients, with a 100% disease control rate by imaging criteria and median overall survival of 13.5 months.

SORAFENIB AND TACE

The mitogen-activated protein kinase (MAPK) pathway, which includes a cascade of phosphorylation events involving multiple kinases and is vital for the transduction of cell proliferation and differentiation signals, is often dysregulated during hepatocarcinogenesis. Upregulated activity of the MAPK pathway has been well documented in HCC.[4,11,12,25]

Sorafenib is a multikinase inhibitor that blocks tumor proliferation by targeting the Raf/MAPK/extracellular signal-regulated protein kinase signaling pathway. It also has antiangiogenic properties by targeting the tyrosine kinase VEGFR-2, VEGFR-3, and plant-derived growth factor receptor β. Sorafenib is the first systemic chemotherapy to demonstrate a survival advantage in patients with HCC and is the only approved systemic therapy for patients with intermediate stage HCC.[26] Combining such an agent—its oral administration makes it even more attractive—with TACE was therefore extremely appealing, especially given the additional synergy between doxorubicin (used in TACE) and sorafenib.

To that end, we conducted the first United States phase II study evaluating the safety of sorafenib combined with

transarterial chemoembolization with doxorubicin-eluting beads (DEB-TACE) in patients with unresectable HCC.[27] Thirty-four patients with Child-Pugh scores A to B7, Barcelona Clinic Liver Cancer classes A to C, Eastern Cooperative Oncology Group status 0 to 1, and treatment naïve, have so far been enrolled in the study and received sorafenib 400 mg twice daily 1 week before DEB-TACE, followed by DEB-TACE in 6-week cycles (sorafenib held 3 days before and after DEB-TACE in the first eight patients). Sorafenib was dosed continuously in the remaining patients. Tumor response was assessed by RECIST and EASL criteria (lack of contrast enhancement) using MRI obtained at baseline and 3 weeks after DEB-TACE and then every 1 to 2 cycles thereafter.

An interim safety assessment performed after the initial eight patients did not reveal any outstanding toxicity, with grade 3 toxicities mostly limited to hand-foot skin reaction (42%) (resolved with dose reduction), right upper quadrant pain (28%), fatigue (28%), lymphopenia (14%), and hypertension (14%). On follow-up imaging, patients who had completed DEB-TACE had 100% objective tumor response by EASL and partial response or stable disease by RECIST (Figure 1). Overall, this preliminary analysis shows that the combination appears to be safe because it did not result in any greater toxicity than with either therapy alone.

FUTURE DIRECTIONS

The rationale for combining antiangiogenic drugs with TACE is abundantly clear. If this combination is proven to be safe and found to increase time to tumor progression, it is very likely that it will become common clinical practice. The data have so far been promising. It should, however, be stressed that further research is necessary to demonstrate a clear survival benefit. This new perspective in the management of patients with unresectable HCC has opened the door for translational studies to identify potential predictive markers of response to this combination therapy and guide patient selection. By the end of 2011, we should have the results of several clinical trials that are currently underway, which will hopefully lead to a more effective treatment for this highly lethal cancer. ■

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