Novel Local Therapies in Hepatocellular Carcinoma

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The incidence of hepatocellular carcinoma (HCC) seems to be on the rise, with more than 500,000 new cases worldwide, most of them being diagnosed as advanced and unresectable at presentation.[1] Patients with advanced unresectable HCC, however, have more treatment options than they did 5 years ago, and the future looks brighter than ever. As systemic and local therapies for unresectable HCC continue to evolve, so does the combination of these two treatment modalities. Moreover, new treatment options have emerged, including injection of oncolytic virus vaccines and new therapeutic targets of HCC metabolism.

In this review, we present an overview of some novel local therapies for unresectable HCC that have been introduced recently to the medical community or are currently under preclinical and initial clinical testing. Because liver transplantation and resection are the only curative options at present for HCC, the long-term goal of all novel therapies must be to effectively downstage patients with unresectable HCC and offer a chance for cure. In order for these novel therapies to be successful and have a significant impact on advanced liver cancer, it is highly likely that they will be employed in combination with other novel or existing therapies. It is also noteworthy that the standard imaging criteria used to characterize HCC tumor response and/or progression may need to further adapt and better define tumor response on a molecular rather than morphological level.

Combination of Intra-arterial Chemoembolization and Antiangiogenic Therapy

Currently, sorafenib is the most popular antiangiogenic agent that is being tested in combination with transcatheter arterial chemoembolization (TACE). Since Pawlik et al. reported on the efficacy of a phase II trial of the combination of drug-eluting beads TACE (DEB-TACE) and sorafenib, encouraging results of the global phase II randomized, double-blind, placebo-controlled SPACE study (sorafenib or placebo in combination with TACE with DEB-TACE) and positive results of the START trial (a phase II study in Asia of the combination of TACE with sorafenib in patients with HCC) have been reported.[2-4] In the SPACE study, which included 307 patients with unresectable intermediate-stage HCC and Child-Pugh A cirrhosis, there was a statistically significant advantage of sorafenib over placebo in time to progression (TTP; median, 169 days; hazard ratio, 0.797; 95% confidence interval, 0.588-1.080; $P = 0.072$).[2] In the START trial, which included 166 patients, the median TTP was 9 months, and only 15% of patients discontinued treatment due to severe adverse events.[3]

Two clinical trials that are currently recruiting patients are the TACTICS trial and the ECOG E1208 trial. The TACTICS trial (ClinicalTrials.gov identifier NCT01217034) is a randomized phase III study led by the Japan Liver Oncology Group in which sorafenib is started at a lower dose (400 mg every other day) and, after tolerability is established, patients resume with the full dose of 400 mg twice daily. In this trial, sorafenib is interrupted 2 days before TACE and resumed at 3 days (and up to 21 days) after TACE. The primary endpoint is time to untreatable progression, as defined by presence of Child-Pugh C cirrhosis, increase in tumor size by 125% from baseline, vascular invasion, and/or extrahepatic spread of more than 10 mm.

The ECOG E1208 trial (ClinicalTrials.gov identifier NCT01004978) is a randomized, double-blind, prospective, multicenter phase III study evaluating the combination of TACE and sorafenib using an interrupted schedule. Prerandomization stratification is performed according to Child-Pugh score (A versus B7), type of TACE (conventional versus

Abbreviations: DEB-TACE, drug-eluting beads transcatheter arterial chemoembolization; HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization.

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DEB-TACE), and presence or absence of macrovascular intrahepatic portal vein invasion. A maximum number of four TACE sessions within 6 months is allowed, after which patients are placed on sorafenib maintenance until disease progression. Patients begin receiving sorafenib 10-14 days prior to TACE to establish dosage and monitor toxicity. Sorafenib is held for 24 to 48 hours before TACE and is resumed 7 to 14 days after each TACE session if certain criteria for toxicities and ECOG performance status are met. The primary objective is progression-free survival with TACE alone or with sorafenib; secondary objectives include overall survival and toxicity, extrahepatic versus intrahepatic patterns of failure, and pharmacogenetic and pharmacokinetic properties of sorafenib.

There is increased interest in testing TACE with other new agents, including brivanib (the BRISK TA study, ClinicalTrials.gov identifier NCT00908752), everolimus (the TRACER study, ClinicalTrials.gov identifier NCT01379521), and axitinib (ClinicalTrials.gov identifier NCT01352728). Not surprisingly, more than 50 clinical trials are currently assessing molecular targeting agents for intermediate and advanced HCC in combination with TACE.

Combination of Intratumoral and Intravenous Injection of Oncolytic Virus

Oncolytic viruses have been designed to exploit tumor-selective viral replication, leading to subsequent tumor cell lysis by mature virons and further infection of tumor cells.[5] One example is the oncolytic virus JX-594, a targeted and transgene-armed oncolytic poxvirus modified by insertion of human granulocyte macrophage colony-stimulating factor (*CSF2*) and *LacZ* genes into the thymidine kinase (*TK*) gene region.[6,7] Selective replication of the virus in cancer cells is driven by cellular epidermal growth factor receptor/Ras pathway signaling, thymidine kinase elevation, and type 1 interferon resistance.

In a phase I trial of intratumoral injection into liver tumors, JX-594 was well tolerated and associated with replication, expression of biologically active *CSF2*, and tumor destruction. The vaccinia virus was also found to be ideally suited for intravenous delivery, as it is resistant to complement and antibody-mediated neutralization in the blood, as shown in a phase I trial of intravenous administration of JX-594.[8] The results of a randomized dose-finding phase II trial in which JX-594 was administered intravenously followed by intratumoral injections in 30 patients with advanced HCC (Clinicaltrials.gov identifier NCT01171651) have been reported recently. Treatment with high-dose JX-594 was associated with prolonged survival versus low-dose JX-594 (median survival, 14.1 months versus 6.7 months; hazard ratio, 0.39; $P = 0.02$).[9] A phase IIb randomized, single-blinded trial of JX-594 plus best supportive care versus placebo plus best supportive care in patients with advanced HCC who have failed sorafenib treatment (the TRAVERSE study, Clinicaltrials.gov identifier NCT01387555) is currently recruiting patients. In this study, patients randomized to JX-594 will receive a dose of 10^9 plaque-forming units intravenously on the first day of treatment, followed by five intratumoral treatments between day 8 and week 18.

Intra-arterial Injection of 3-Bromopyruvate

The pyruvate analog 3-bromopyruvate is an alkylating agent and a potent inhibitor of glycolysis. Because cancer cells depend on glycolysis for their energy requirements, 3-bromopyruvate appears to be a potent new antiglycolytic anticancer treatment option.[10] The primary mechanism of 3-bromopyruvate's action is thought to occur via preferential alkylation of glyceraldehyde 3-phosphate dehydrogenase, and 3-bromopyruvate–mediated cancer cell death is linked to generation of free radicals, endoplasmic reticulum stress, and inhibition of global protein synthesis.[11] 3-Bromopyruvate has been tested successfully in many animal tumor models, and preparations for a phase I study of intra-arterial injection of 3-bromopyruvate for unresectable liver cancer is currently underway.

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