Transarterial Sorafenib Chemoembolization: Preliminary Study of Technical Feasibility in a Rabbit Model

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ABSTRACT

Purpose: To test the feasibility of targeted intraarterial administration of the tyrosine kinase inhibitor chemotherapeutic agent sorafenib to inhibit embolotherapy-induced tumor angiogenesis and reduce systemic drug side effects.

Materials and Methods: The left hepatic lobes of five New Zealand White rabbits (mean weight, 2.7 kg ± 0.2) were treated with chemoembolization with sorafenib and ethiodized oil emulsion, followed by immediate euthanasia. Postprocedure noncontrast computed tomography (CT) was used to evaluate intrahepatic chemotherapy mixture distribution. Liquid chromatography/tandem mass spectrometry (LC-MS/MS) was then used to directly measure sorafenib concentration in the treated liver tissue. Histopathologic assessment of treated left lobes was performed to identify any immediate toxic effects of the sorafenib solution.

Results: Lobar sorafenib chemoembolization was successfully performed in all cases via the left hepatic artery. Sorafenib and ethiodized oil (mean, 6.4 mg ± 3.8 and 0.95 mL ± 0.7, respectively) were injected, and CT confirmed targeted left hepatic lobe sorafenib emulsion delivery in all cases. Corresponding LC-MS/MS analysis yielded a mean sorafenib concentration of 94.2 μg/mL ± 48.3 in treated left lobe samples (n = 5), significantly greater than typical therapeutic drug levels (2–10 μg/mL) achieved with oral sorafenib systemic therapy. Histopathologic assessment showed only mild or moderate nonspecific ballooning degeneration in zone 3 hepatocytes, without tissue necrosis.

Conclusions: Targeted transarterial sorafenib delivery is feasible and results in higher tissue drug levels than reported for systemic sorafenib therapy, without immediate histopathologic tissue toxicity. Future studies should aim to determine the utility of sorafenib chemoembolization in reducing hypoxia-induced vasculogenesis in liver tumors.

ABBREVIATIONS

C_{max} = peak plasma concentration, HCC = hepatocellular carcinoma, HIF = hypoxia-inducible factor, LC-MS/MS = liquid chromatography/tandem mass spectrometry, SRM = selected reaction monitoring, UHPLC = ultra–high-pressure liquid chromatography, VEGF = vascular endothelial growth factor, VEGFR = vascular endothelial growth factor receptor

Transarterial chemoembolization takes advantage of the hepatic arterial derivation of hepatocellular carcinoma (HCC) perfusion for targeted chemotherapeutic agent delivery and tumor devascularization (1). Although embolization of hepatic arteries supplying liver malignancies results in hypoxia and tumor necrosis, this process also induces angiogenesis (2). Induction of ischemia within liver neoplasms has been shown, in rabbit models, to result in increased intratumoral expression of hypoxia-inducible factor (HIF)–1α among residual surviving cells (3). When combined in cellular nuclei with HIF-1β, operational HIF-1 is formed and initiates a cascade of gene expression of proangiogenic factors and altered glucose metabolism to counteract nutritional deprivation incipient with hypoxia (2). The array of upregulated factors is diverse, but prominently features vascular endothelial growth factor (VEGF), which results in aggressive tumor ontogenesis and vascularity (4)

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and connotes increased tumoral propensity for metastasis and invasive behavior (5). VEGF exerts its downstream effects by interaction with a tyrosine kinase receptor, designated VEGF receptor (VEGFR).

Receptor tyrosine kinase inhibitors are a class of drugs that interrupt signaling pathways involved in tumor progression and angiogenesis (6). In biochemical assays and murine models, sorafenib (BAY 43-9006; Nexavar; Bayer, Leverkusen, Germany) has been shown to potently inhibit multiple receptor tyrosine kinases, including VEGFR subtypes, involved in tumor angiogenesis. Immunohistologic correlation with murine tumors in mice treated with sorafenib demonstrates a decrease in tumoral microvessel density (6), and in vitro assays and murine models have demonstrated suppression of HCC cell proliferation and induction of apoptosis in a dose-dependent manner (7). Clinically, sorafenib has been used in the treatment of patients with advanced HCC. Double-blind randomized controlled phase 3 clinical trials of sorafenib in such patients have shown delay in time to progression and increase in overall survival (8,9). However, the adverse effect profile of this agent, which is at present commercially available only as an oral formulation for systemic delivery, limits medication compliance, with notable side effects including diarrhea and hand–foot syndrome that occur at a statistically significantly higher rate than in placebo comparisons (8). To date, other routes of sorafenib instillation have not been widely explored; the ability to infuse sorafenib by using a transcatheter intraarterial route has the potential to deliver high localized drug concentrations directly to tumor to reduce the proangiogenic cascade stimulated by hypoxic conditions precipitated during chemoembolization while decreasing systemic drug side effects. As such, the goal of the present project was to assess the feasibility of transarterial hepatic delivery of a lipid-emulsified preparation of sorafenib in a rabbit model.

MATERIALS AND METHODS

Animal care and use committee approval was obtained for this prospective study. The experimental protocol consisted of several steps: (i) production of a lipid-emulsified sorafenib preparation, (ii) in vivo intravascular delivery of the agent into New Zealand White rabbit livers, (iii) noninvasive assessment of ethiodized oil and drug emulsion delivery by computed tomography (CT) imaging, (iv) liver explantation and liquid chromatography (LC)/tandem mass spectrometry (LC-MS/MS) direct tissue chemotherapeutic analysis to determine local drug concentrations, and (v) histopathologic analysis to assess for possible toxic effects of sorafenib solution on hepatic parenchyma.

Intraarterial Dosing and Preparation of Sorafenib Solution

In devising a dosing regimen for intraarterial sorafenib, peak plasma concentrations (C_{max}) and therapeutic drug levels for humans and rabbits were considered. In human trials, the C_{max} for sorafenib, as demonstrated in multiple discontinuous (10) and continuous (11) dosing trials that used the maximum tolerated dosage consisting of oral sorafenib 400 mg twice daily (a regimen widely used clinically), ranged from approximately 2 to 10 μg/mL; these plasma concentrations represent therapeutic levels of sorafenib, which inhibits components of the Raf–mitogen-activated protein kinase kinase–extracellular signal-related kinase signaling pathway and receptor tyrosine kinases at concentrations ranging between 3 and 270 ng/mL (10). In rabbits, plasma sorafenib levels approximating 5 μg/mL (a concentration comparable to C_{max} achieved in clinical studies) may be reasonably attained by using an oral dosing regimen of 30 mg/kg/d (Bayer, unpublished data, February 2011). Considering that chemoembolization generally results in local drug concentrations 10–100 times greater than systemic administration 1), intraarterial dosing was therefore empirically targeted at approximately 3 mg/kg. The selected chemoembolization protocol consisted of a 6–12-mg/mL–concentration sorafenib solution emulsified with an equal volume of ethiodized oil (Lipiodol; Guerbet, Villepinte, France), and required injection of 1.5–3 mL total chemotherapeutic emulsion volume for complete dose administration in a 3.0-kg rabbit.

Sorafenib liquid solution formulation was prepared by using a solvent of 12.5% Cremophor EL (Sigma-Aldrich, St. Louis, Missouri), 12.5% ethyl alcohol (Sigma-Aldrich), and 75% distilled water (Sigma-Aldrich) (6). For solution preparation, sorafenib powder (provided by Bayer) was dissolved in a 50% Cremophor EL and 50% ethyl alcohol mixture at 12–24 mg/mL. Heating of the mixture to 60°C was necessary to get the sorafenib into solution. When the compound was in solution, distilled water was added gradually with mixing to generate the 6–12-mg/mL dosing solution. The sorafenib solution was then allowed to cool to room temperature before use in chemoembolization procedures.

Transarterial Sorafenib Chemoembolization

Five male New Zealand White rabbits (mean weight, 2.7 kg ± 0.2) underwent sorafenib chemoembolization procedures, which were performed by a single operator (R.C.G.) after rabbits were intubated and maintained under general anesthesia (induction with intramuscular ketamine 50–65 mg/kg and intramuscular xylazine 5 mg/kg, maintenance with inhaled isoflurane 1%–3%). Angiography was performed with a C-arm unit (OEC Medical Systems series 9600; GE Healthcare, Milwaukee, Wisconsin). The femoral artery was accessed through a surgical cutdown and catheterized with a 3-F vascular sheath (Cook, Bloomington, Indiana). A 2-F JB1 catheter (Cook) was advanced over a guide wire, and the celiac artery was selectively catheterized. The catheter was then advanced into the left hepatic artery. Celiac and hepatic arteriography was performed via injections of iohexol (Omnipaque-300;