LABORATORY INVESTIGATION

Transarterial Chemoembolization Using Sorafenib in a Rabbit VX2 Liver Tumor Model: Pharmacokinetics and Antitumor Effect

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ABSTRACT

Purpose: To investigate feasibility, safety, and effect of transarterial chemoembolization using sorafenib on degree of tumor necrosis in a rabbit VX2 liver tumor model.

Materials and Methods: New Zealand White rabbits (n = 20) with a VX2 tumor were divided into two groups; one group was treated with hepatic arterial administration of 0.5 mL ethiodized oil alone (Lipiodol; Guerbet, Aulnay-sous-Bois, France) (transarterial embolization with Lipiodol [TAE-L] group), and one group was treated with 0.5 mL ethiodized oil plus 10 mg sorafenib (transarterial embolization with sorafenib [TAE-S] group). Liquid chromatography tandem mass spectrometry was used to measure sorafenib concentration in peripheral blood and tissue. Hepatic enzymes, vascular endothelial growth factor (VEGF), and hypoxia-inducible factor 1α (HIF-1α) were measured at 0, 24, and 72 hours after treatment. Histopathologic examination was performed to evaluate extent of tumor necrosis and normal parenchymal damage.

Results: Serum sorafenib concentration peaked at 2 hours after treatment. The mean tissue concentration was 406.8 times greater than the serum concentration. Aspartate aminotransferase and alanine aminotransferase levels were significantly elevated in the TAE-S group at 24 hours after treatment. Serum VEGF and HIF-1α concentrations were not significantly different between the TAE-L and TAE-S groups. Hepatic parenchymal damage was more severe in the TAE-S group. Mean fraction of tumor necrosis after treatment was significantly greater in the TAE-S group.

Conclusions: Transarterial chemoembolization using sorafenib resulted in a high intrahepatic concentration of sorafenib. The degree of tumor necrosis was significantly greater in the TAE-S group compared with the TAE-L group, but more severe toxicity of normal liver tissue also occurred.

ABBREVIATIONS

ALT = alanine aminotransferase, AST = aspartate aminotransferase, HCC = hepatocellular carcinoma, HIF-1α = hypoxia-inducible factor 1α, m/z = mass-to-charge ratio, TAE-L = transarterial embolization with Lipiodol, TAE-S = transarterial embolization with sorafenib, VEGF = vascular endothelial growth factor

Transarterial chemoembolization is an established treatment for unresectable hepatocellular carcinoma (HCC) that significantly improves survival (1). It can deliver high doses of chemotherapeutic agents to the tumor and induce ischemic necrosis via arterial embolization. Transarterial chemoembolization results in hypoxia and tumor necrosis; however, this hypoxia can also enhance angiogenesis and chemoresistance of HCC and result in resistance to transarterial chemoembolization (2). If transarterial chemoembolization does not induce

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complete necrosis of the tumor, the residual surviving cancerous tissue overexpresses vascular endothelial growth factor (VEGF) (3). A more recent study revealed that preoperative transarterial chemoembolization confers a poor prognosis in patients with HCC through activation of hypoxia-inducible factor 1α (HIF-1α) (4). Thus, inhibition of angiogenesis is critical for successful treatment of HCC.

Sorafenib (Nexavar; Bayer, Leverkusen, Germany) is a multiple-receptor tyrosine kinase inhibitor that interrupts signaling pathways involved in tumor progression and angiogenesis (5). It is the first orally administered agent reported to improve survival of patients with unresectable advanced disease (6,7). Although it has a survival benefit, sorafenib also has systemic adverse effects (eg, diarrhea, hand-foot skin reaction, anorexia, weight loss). Some patients are unable to tolerate treatment because of these adverse effects, which results in dose reduction, dose interruption, or participant dropout (6).

Theoretically, transarterial administration and delivery of sorafenib to the liver should induce an antiangiogenic effect that is localized in the liver. It should also prevent transarterial chemoembolization–induced angiogenesis and tumor growth, with fewer adverse systemic effects. Only a few studies using a normal liver model have investigated the feasibility of transarterial administration of sorafenib (8,9). Only a few reports have described pharmacokinetics, safety, and degree of tumor growth after administration of sorafenib in VX2 tumor models (10,11).

The relationships between sorafenib and angiogenetic factors (eg, VEGF and HIF-1α) have been investigated in some laboratory and clinical studies (12–15); the results of these studies are controversial. To the best of our knowledge, the role of VEGF and HIF-1α as biomarkers has not been studied quantitatively, in combination, during intraarterial administration of sorafenib. The aim of this study was to investigate the feasibility, safety, and effects on angiogenesis factors as biomarkers and necrosis after transarterial chemoembolization with sorafenib, using a rabbit VX2 tumor model.

MATERIALS AND METHODS

Animals

The animal protocol for this study was approved by our institutional animal care and use committee. The study population consisted of 20 male New Zealand White rabbits (body weight, 2.9–3.4 kg). The VX2 carcinoma strain had been maintained by means of successive transplantation of tumor cells into the hind limbs of carrier rabbits. Anesthesia was induced through intravenous injection of 50 mg/kg ketamine hydrochloride (Ketamine; Yuhan Corporation, Seoul, Korea) and 0.1 mg/kg 2% xylazine (Rompun; Bayer). A midline abdominal incision was used to expose the left lateral lobe of the liver. A single 1-mm^3 tumor chip was implanted at a depth of 5 mm from the liver capsule. After implantation, hemostasis was achieved by applying gentle pressure with a cotton swab to allow the growth of a single, well-demarcated tumor in the liver of each recipient rabbit. Chemoembolization was performed 2 weeks after tumor implantation, which is when the tumors were expected to have increased in size to 2 cm in diameter.

Treatment Procedure

The rabbits were randomly divided into two groups with 10 rabbits in each group. One group was treated with intraarterial administration of ethiodized oil (Lipiodol; Guerbet, Aulnay-sous-Bois, France) alone (transarterial embolization with Lipiodol [TAE-L] group). The other group was treated with intraarterial administration of sorafenib in a Lipiodol solution (transarterial embolization with sorafenib [TAE-S] group). Considering the generally accepted maximum dose of Lipiodol (10 mL in a single session of transarterial chemoembolization) and assuming the weight of a rabbit as one twentieth of an adult human, we used a 0.5-mL target dose of Lipiodol. In a rabbit, oral administration of 30 mg/kg/d sorafenib can achieve therapeutic plasma concentrations approximating 5 μg/mL (8). Considering that chemoembolization generally results in local drug concentrations that are 10–100 times greater than concentrations resulting from systemic administration (8), the intraarterial sorafenib dose was targeted at 3 mg/kg. The sorafenib in a Lipiodol solution was prepared by dissolving sorafenib in Lipiodol to obtain a concentration of 20 mg/mL (ie, 10 mg/0.5 mL/rabbit). The formulation was prepared using sonication of the mixture for 15 minutes at room temperature.

Transarterial embolization was performed under fluoroscopy guidance 2 weeks after implantation of the VX2 carcinoma. After anesthesia was induced as described earlier, the right ear artery was punctured percutaneously, and a 4-F introducer (Micropuncture Access Set; Cook, Inc, Bloomington, Indiana) was inserted. Using a 2-F microcatheter (PROGREAT; Terumo, Tokyo, Japan) and guide wire (ASAHI Meister; Asahi Intecc Co, Ltd, Aichi, Japan), celiac angiography was performed to identify hepatic arterial anatomy and the tumor. After selection of the left hepatic artery, 0.5 mL Lipiodol (TAE-L group) or 0.5 mL sorafenib in a Lipiodol solution (TAE-S group) was infused in microboluses. The microcatheter was flushed using normal saline until the radiopaque Lipiodol was completely delivered into the hepatic artery. The catheter was then removed, and hemostasis was obtained using manual compression.

Measurement of Serum and Tissue Sorafenib Concentrations

Whole blood was collected and centrifuged for pharmacokinetics and biochemical assays (0.5 mL for biochemical

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