LABORATORY INVESTIGATION

Effect of Transcatheter Intra-Arterial Therapies on Tumor Interstitial Fluid Pressure and Its Relation to Drug Penetration in a Rabbit Liver Tumor Model

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ABSTRACT

Purpose: To determine the change in tumor interstitial fluid pressure (IFP) after transcatheter intra-arterial (IA) therapies and its relation to drug penetration in liver cancer.

Materials and Methods: VX2 tumors were grown in the livers of 16 rabbits. The rabbits were treated with intravenous injection of doxorubicin (group 1; n = 4), hepatic IA injection of doxorubicin (group 2; n = 4), hepatic IA injection of doxorubicin followed by embolization with polyvinyl alcohol particles (group 3; n = 4), or hepatic IA injection of doxorubicin mixed with Lipiodol followed by polyvinyl alcohol embolization (group 4; n = 4). Tumor IFP was measured with a Mikro-Tip pressure catheter before and 1 hour after treatment. Doxorubicin penetration was evaluated by immunofluorescence.

Results: Tumor IFP after treatment decreased by 5.0% ± 2.8, 3.9% ± 9.0, 27.1% ± 5.2, and 31.8% ± 7.4 in groups 1–4, respectively. The difference in IFP reduction between embolization-treated groups (groups 3 and 4) and nonembolized groups (groups 1 and 2) was significant ($P < .001$). Doxorubicin penetration distances were 20.3 μm ± 3.7, 45.7 μm ± 10.5, 69.5 μm ± 9.3, and 47.9 μm ± 6.4 in groups 1–4, respectively. IFP reduction was significantly correlated with doxorubicin penetration distance ($r = .671$, $P = .004$).

Conclusions: A greater reduction of tumor IFP was associated with embolization in a preclinical liver tumor model, and embolization may indirectly contribute to increased drug penetration.

ABBREVIATIONS

IA = intra-arterial, IFP = interstitial fluid pressure, IV = intravenous, MVD = microvessel density, PVA = polyvinyl alcohol

Transcatheter intra-arterial (IA) therapies are currently recognized as effective palliative therapies for unresectable primary and metastatic liver cancer, for which hepatic artery chemotherapeutic infusion is an important therapeutic component (1). The rationale for the chemotherapeutic infusion–based transcatheter therapies comes from the observations that direct injection of chemotherapeutic agents into the tumor-feeding arteries improves tumor drug concentration (2) and that subsequent embolization of the arteries reduces drug washout and prolongs the contact between the drugs and cancer cells (3). Recently, transcatheter therapies, especially embolization, have been shown to enhance drug penetration in liver cancer (4). However, the mechanism remains unclear.

Interstitial fluid pressure (IFP) is an important factor that affects drug penetration in tumor. Studies have shown that many solid tumors have an elevated IFP, which forms a physiologic barrier to drug delivery (5). Drug transport across tumor vasculature into tumor interstitium is dependent on the hydrostatic and osmotic

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pressure differences between capillaries and interstitium. Not only does the elevated IFP decrease the net outward filtration pressure from capillaries or even reverse the outward pressure, but it can compress blood vessels and thereby reduce the blood flow to the tumor, which effectively suppress transvascular drug transport (5,6). Various pharmacologic and physical methods have proven to lower tumor IFP, including compounds, irradiation, hyperthermia, high-intensity focused ultrasound, hyperbaric oxygen therapy, and photodynamic therapy (7). The decrease in IFP was accompanied by an increase in intratumoral drug uptake or distribution (7). These findings highlight the effect of IFP on the tumor and its associated influence on cancer therapy.

In transcatheter chemoembolic therapies, the tumor-feeding arteries are purposely blocked to induce ischemia/hypoxia tumor necrosis. It is possible that the tumor IFP changes following the blockade of blood flow. However, little information is available regarding this issue. We hypothesize that transcatheter techniques can modify tumor IFP and thereby improve drug penetration in liver cancer. Therefore, we conducted an experimental study to determine the change of IFP before and after transcatheter IA therapies and its relation to drug penetration.

MATERIALS AND METHODS

Animal Model, Magnetic Resonance Imaging, and Study Groups

The present study was approved by the animal care and use committee of our institution. Adult New Zealand White rabbits (body weight, 2.5–3.0 kg) were purchased from the Center for Experimental Animals of Huazhong University of Science and Technology. The strain of VX2 tumor was maintained by successive implantation into the thigh of carrier rabbits. Tumor implantation was performed by using an aseptic technique, and general anesthesia was introduced with intravenous (IV) sodium pentobarbital (30 mg/kg body weight). Briefly, the rabbit liver was exposed with a midline subxiphoid incision, and then a fresh tumor fragment 1 mm^3 in size was implanted 10 mm deep into the left liver lobe. The abdominal wall was sutured in two layers.

Seventeen days after tumor implantation, all animals underwent magnetic resonance (MR) imaging with a 1.5-T system (MAGNETOM Avanto; Siemens, Erlangen, Germany) to detect formation and size of the liver VX2 tumor. MR imaging examinations were performed with the rabbit in the supine position and included the entire liver. Transverse T2-weighted images were acquired by using a turbo spin-echo sequence (repetition time/echo time, 3,700/87 ms; section thickness, 4 mm; intersection gap, 15%; bandwidth, 168 Hz/pixel; matrix, 320 × 320). The volume of tumor was calculated according to the equation $V = \pi/6 \times (ab^2)$, where a is the largest diameter of the tumor and b is the smallest.

A total of 16 animal models of VX2 liver tumor were established. The animals were then randomly assigned into four groups of four rabbits each and treated with IV injection of 8 mg/kg doxorubicin (Actavis Italy, Nerviano, Italy; group 1), hepatic IA injection of doxorubicin (group 2), hepatic IA injection of doxorubicin followed by embolization with 150–250 μm polyvinyl alcohol (PVA) particles (Cook, Bloomington, Indiana; group 3), or hepatic IA injection of a mixture of doxorubicin with Lipiodol (Guerbet, Roissy, France) followed by PVA embolization (group 4).

Transcatheter Procedure

One day after MR imaging, animals underwent the transcatheter procedure. Access was obtained into the common femoral artery via an open puncture with an 18-gauge needle, after which a 4-F sheath (Terumo, Tokyo, Japan) was inserted. The celiac axis was cannulated with a 4-F Cobra catheter (Terumo), and then a 2.7-F microcatheter (Terumo) was advanced coaxially to the common hepatic, proper hepatic, and left hepatic arteries in sequence. After the tumor was confirmed to be supplied by the left hepatic artery, transcatheter therapies were subsequently performed. Doxorubicin powder 8 mg/kg was dissolved in advance in 1 mL of 0.9% saline solution or mixed with 0.4 mL of Lipiodol. The doxorubicin solution or doxorubicin/Lipiodol emulsion was slowly injected under direct fluoroscopy for approximately 1 minute to minimize reflux of the drug. For embolization groups, a vial of 150–250-μm PVA particles was reconstituted with 10 mL of contrast medium and the embolization was done immediately after doxorubicin injection, with an embolization endpoint of artery occlusion (**Fig 1**). For the systemic IV therapy group, the injection of doxorubicin solution was done via the ear vein.

IFP Measurement

Two 3.5-F Millar Mikro-Tip pressure catheters and PowerLab data acquisition systems (ADInstruments, Bella Vista, Australia) were used to measure IFP. When hepatic artery catheterization had been completed, an abdominal incision was made and the tumor-bearing liver lobe was exposed. One pressure catheter was then inserted as close to the center of the tumor as possible, and the other was inserted 1 cm deep into the adjacent normal liver tissue. The time interval between anesthesia induction and initiation of IFP measurement was approximately 30 minutes. The tumor access point of the pressure catheter was selected, and the direction and depth of catheter insertion was chosen based on previous MR image review, intraprocedural palpation, and visual observations. The tumor IFP was measured before and 1 hour after treatment; whereas the IFP in the adjacent liver tissue was measured only before treatment. To