Development of MRI-Guided Intrabiliary Local Agent Delivery Technique

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PURPOSE: Malignant obstructive jaundice is a common clinical entity associated with a wide spectrum of pancreatobiliary diseases. Intrabiliary delivery of therapeutic agents into bile duct walls may provide a new approach to effectively treat malignant pancreatobiliary diseases. As an initial step, this study was to develop a novel technique of using MRI to monitor intrabiliary local delivery of an intracellular T1 MR contrast agent, motexafin gadolinium (MGd, Pharmacyclics, Inc.), into common bile duct (CBD) walls of pigs.

METHODS: The study was divided into three portions. In the first portion, we evaluated, in vitro, the capability of MGd to enter human cholangiocarcinoma cells (Mz-ChA-1). Seven groups of Mz-ChA-1 cells were treated by adding MGd at various concentrations of 0, 25, 50, 75, 100, 125, and 150μg/mL for 48 hours. Cells were then dispersed in 0.6-mL eppendorf tubes with 1% agarose. In vitro 3T MRI of these MGd-cell-containing tubes was achieved with T1-weighted imaging (T1WI) (spin echo (SE) and TR/TE=550/12ms). We then measured MR signal intensity (SI) of each tube. Other groups of Mz-ChA-1 cells were treated by MGd at the same concentrations as described above, fixed with 4% paraformaldehyde, counterstained with DAPI, and then examined with a laser confocal microscope.

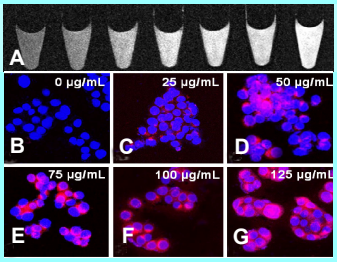

Fig. 1. (A) In vitro T1WI MRI of Mz-ChA-1 cells treated by MGd at different concentrations, showing increased bright signals with increasing MGd concentrations. (B-G) Confocal microscopy of Mz-ChA-1 cells treated with MGd at different concentrations (C-G), showing increased intracellular uptake of MGd, shown as pink, with increasing MGd concentrations.

In the second portion, serial ex vivo experiments were conducted to establish the surgical protocol for intrabiliary delivery of MGd into pig CBD walls. Six cadaveric livers with entire bile ducts and portion of duodenum were harvested from pigs. Accessing through the cystic duct, a custom-made microporous balloon catheter was positioned into the CBD, where 3-mL MGd (0.5mg/mL) mixed with trypan blue was locally infused into the walls of three CBDs. Additional three CBDs were infused with saline to serve as control. Ex vivo 3T MRI of these CBDs were performed with fat-suppressed T1WI (SE, TR/TE=550/12ms). After MR imaging, the CBD specimens were cryosectioned for histologic correlation and confirmation.

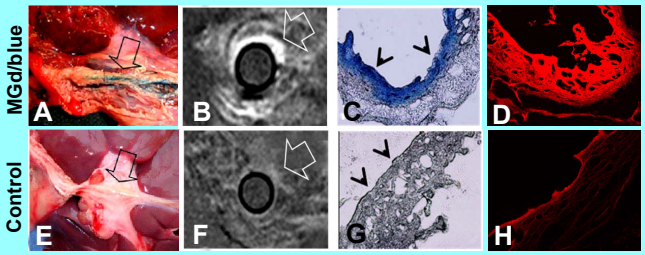

Fig. 2. (A-D) Ex vivo intrabiliary delivery of MGd/blue. (A) Surgery shows blue-colored CBD; (B) Axial MRI demonstrates the penetration of MGd into the CBD wall/peri-CBD tissue (arrow B); and (C&D) Microscopy confirms blue-stained CBD wall (arrowheads) with red-fluorescent MGds through the CBD/peri-CBD region. These findings are not seen in control CBD (E-H).

In the third portion, an in vivo study was designed to validate the feasibility of using MR to monitor intrabiliary delivery of MGd into the pig CBD wall. After a subcostal laparotomy, a microporous balloon catheter was positioned into CBD through a transcystic access under X-ray fluoroscopic guidance. Three-mL MGd (0.5mg/mL) mixed with trypan blue was then intrabiliarily infused into the CBD wall. Before and after intrabiliary MGd/blue infusion, axial and coronal 3T MRI of the CBD was performed using fat-suppressed T1WI (turbo field echo(TFE), TR/TE=10/3ms, flip angle 15°) with comparison between a surface coil and a 0.032-inch intrabiliary MR imaging-guidewire (MRIG). Subsequently, the CBD specimen was harvested and cryosectioned for MRI-histologic correlation and confirmation.

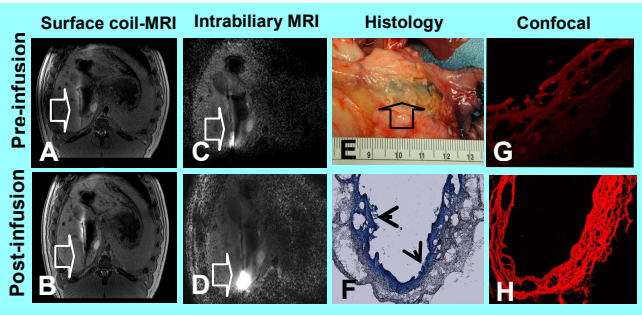

Fig. 3. In vivo MRI of intrabliary balloon-mediated local delivery of MGd/blue. Both surface coil-MRI (A&B) and intrabiliary MRI (C&D) demonstrate MGd-enhanced CBD region (arrows) after intrabiliary MGd/blue infusion. (E) Surgery shows blue-stained CBD (arrow on E), which is confirmed by histologic correlation as blue-stained CBD wall (arrowhead on F) with red fluorescence in the CBD wall containing MGd (H, confocal imaging). No red fluorescence was found in the CBD wall without MGd (G)

RESULTS: Of the in vitro experiments, MGd presented its intracellular capability for Mz-ChA-1 cells, which was confirmed by (i) T1WI MRI as a linear increase of SI; and (ii) confocal microscopy as increased intracytoplasm pink dots from 25 to 75 μg/Ml MGd (Fig. 1). Of the ex vivo experiments, we successfully established the surgical protocol to deliver MGd/blue into the CBD walls (Fig. 2). Of the in vivo study, MRI demonstrated MGd-enhanced CBD wall/peri-CBD region after intrabiliary MGd-infusion, which was confirmed by histologic correlation (Fig. 3).

CONCLUSIONS: This study initially confirms the ability of MGd to enter human cholangiocarcinoma cells and demonstrates the feasibility of using MRI to monitor the intrabiliary delivery of MGd into CBD walls. This new technique may open new avenues for MR-guided intrabiliary local delivery of therapeutic agents, such as genes and drugs, to treat malignant pancreatobiliary diseases.