Potential of SPIO in the differential diagnosis of bone metastasis and inflammation - animal experiments

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Synopsis

We investigated the potential of superparamagnetic iron oxide (SPIO) in the differential diagnosis of bone metastasis and inflammation using the animal models. VX2 tumor cells or croton oil were injected into the femora of rabbits. SPIO was intravenously injected at a dose of 8 micro mol Fe/kg. The signal intensity of tumor did not change after a SPIO injection, whereas signal intensity of normal bone marrow and inflammation decreased. Our results showed that SPIO was useful to detect bone marrow tumors. In addition, SPIO may have potential in the differential diagnosis of bone metastasis and inflammation.

Methods

Animal experiments: Six rabbits were inoculated with 0.3 mL of VX2 tumor into the right distal femora (VX2 group). The other six rabbits were inoculated with 0.3 mL of 10 % croton oil into the right distal femora to induce inflammation. As a control, the left femora of all rabbits were left intact. At 12 to 14 days after tumor or croton oil implantation, all rabbits underwent MR imaging study.

MR imaging: The rabbits were subjected to MR examination using a 1.0 T clinical imager (Magnetom, Harmony, SIEMENS). The spin-echo and 2D-FLASH were selected for the SPIO-enhanced bone marrow imaging. Before and at 24 hours after the injection of ferucarbotran (Resovist, Schering AG), MR images of both femora were examined using a spin-echo sequence (TR / TE = 3000 / 40, 50, 60, 80 msec) with the following parameters: FOV 180 × 113 mm, Matrix 256 × 160, 26 slices of 3 mm thickness, one excitation. To examine the distribution of SPIO in bone marrow at the dynamic phase, ferucarbotran enhanced 2D-FLASH (TR / TE = 30 / 20 msec, FA 30º) were obtained with the following parameters: FOV 180 × 113 mm, Matrix 256 × 80, 2 slices of 3 mm thickness, and one excitation, actual acquisition time of 3.6 sec per image. Thirty-five images, including the 5 precontrast measurements, were continuously taken at intervals of 3.6 seconds up to 108 seconds after injection. Ferucarbotran was injected at a dose of 8 micro mol Fe/kg immediately after acquisition of the fifth measurement.

Data Analysis: Signal intensity (SI) of normal bone marrow, tumor, and inflammation regions were measured. The relative enhancement (RE) of bone marrow in each group was calculated using the following equation: RE(%) = [(SIpost-SIpre)/(SIpre)]×100, where SIpre and SIpost are the signal intensities of bone marrow before and after ferucarbotran injection.

Histological analysis: After MR imaging, the rabbits were sacrificed, and both femora were removed. The femora were fixed in phosphate-buffered 10 % formalin. The sections were embedded in paraffin blocks. Sections from each paraffin block were stained with HE for histological examination.

Statistical Analysis: RE differences in the bone marrow, tumor, and inflammation after ferucarbotran injection were statistically examined by the Tukey test.

Results and Discussion

Bone marrow in the control and croton groups was detected as a hypointense region after a ferucarbotran injection, whereas the MR images did no change between precontrast and postcontrast bone marrow in the VX2 group (Fig.1). Although the RE of bone marrow in the control and croton groups gradually decreased after a ferucarbotran injection, the RE of bone marrow in the VX2 group was unchanged. The signal change profile in the control and croton groups was completely different from the transient change clinically observed in the arterial phase of dynamic MR imaging and perfusion studies using Gd-contrast agents based on blood flow. Ferucarbotran is phagocytosed by Kupffer cells (i.e. macrophages) after intravenous injection and the signal change in liver MR images persists for several hours. The signal intensity profile seemed attributable to the distribution quantity of ferucarbotran in the bone marrow but not the blood flow, as SPIO was reported to accumulate in the bone marrow. Therefore, the difference in the signal intensity profile between tumors and inflammation was considered to represent a difference in ferucarubotran uptake by macrophage.Bone marrow in the control and croton groups was detected as a hypointense region as well as in 2D-FLASH images, whereas MR images did not change between precontrast and postcontrast bone marrow in the VX2 group (Fig.2). Although the RE of bone marrow in the control and croton groups was markedly decreased at 24 hours after ferucarbotran injection, the RE of bone marrow in the VX2 group was unchanged. The RE of bone marrow in the VX2 group was significantly higher than in the control and croton groups using the Tukey test ($p<0.01$). Therefore, this result suggested that ferucarbotran distributed in normal and inflammatory bone marrow, and did not distribute in bone metastasis at even 24 hours after ferucarbotran injection. As the tumor signal profile was completely different from that of inflammation or the normal state at immediately and 24 hours after injection, ferucarbotran-enhanced bone marrow MR imaging might not only have the potential to detect tumors but also could differentiate the tumor from inflammation. Furthermore, ferucarbotran is an excellent contrast agent with a wide imaging window, because its efficacy persists at 24 hours after injection. In histological findings, typical normal bone marrow cells (such as erythroblasts, granulocytes, and megakaryocytes) were observed in bone marrow of the control group (Fig.1). The tumor cells were widely spread in the bone marrow in the VX2 group, but there were few normal hematopoietic cells. Pseudoeosinocyte infiltration was induced in the bone marrow of the croton group, and cell density was higher than in the control group. Macrophages accumulate in the inflammatory region and act as scavengers by phagocytosing the inflammatory substance and necrosis cells. In general, macrophages are generated in bone marrow with inflammation. Therefore, intravenously injected ferucarbotran was phagocytosed by macrophages in bone marrow with inflammation. As a result, the signal intensity of bone marrow in the croton group would decrease, similar to the control group.

In conclusion, in our animal examinations, ferucarbotran was useful to detect tumors in bone marrow at a dose of 8μmol Fe/kg, within the range of the clinical dose for liver MR imaging. In addition, ferucarbotran-enhanced bone marrow imaging has the potential to differentiate bone metastasis from inflammation.

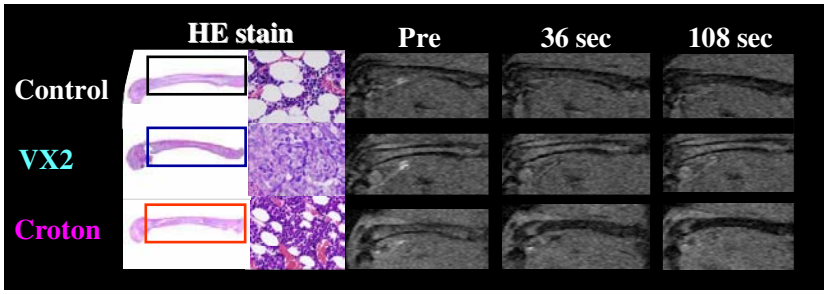

Fig.1 Signal change of bone marrow on 2D-FLASH images at dynamic phase after a ferucarbotran injection at a dose of 8 micro mol Fe/kg.

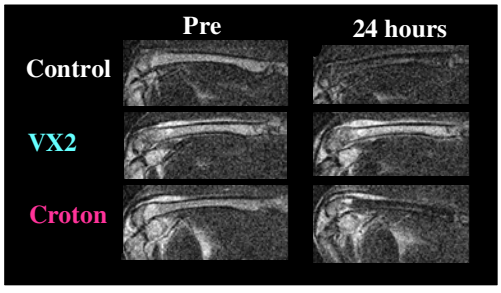

Fig.2 Signal change of bone marrow on the spin-echo images at 24 hours after a ferucarbotran injection at a dose of 8 micro mol Fe/kg.