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Efficacy of Dynamic MRI with Superparamagnetic Iron Oxide (SH U 555 A): Vascularity Evaluation in Hepatocellular Carcinoma

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Purpose: A study was conducted to determine the possibility of evaluating the blood flow in cases of hypervascular hepatocellular carcinoma (HCC) by employing dynamic MRI with superparamagnetic iron oxide (SH U 555 A), which can be rapidly injected via an intravenous route.

Methods: Six patients with hypervascular HCC (23 nodules) served as the subjects. Dynamic MRI includes images obtained at precontrast and at 10 (perfusion phase), 60, 120, 180, 240, 300 and 600 s after the start of injection of SH U 555 A. CT hepatic arteriography (CTHA) and CT during arterial portography (CTAP) were used as the standards of reference, and these were performed in all patients three days after dynamic MRI. The signal changes were evaluated at each phase, especially at the perfusion phase from the viewpoints of a lesion-to-liver contrast-to-noise ratio (CNR) and visual examination.

Results: A total of 23 hypervascular HCC were detected on CTHA and CTAP. Of the 23 lesions, 17 were detected on SH U 555 A enhanced MRI. Incorrect timing during acquisition of the perfusion phase was considered in two cases with three lesions. Of 14 lesions, excluding two cases with incorrect timing, a reduction in the transient signal in the lesions at the perfusion phase was visually recognized in 10 lesions (71%). Significant differences were seen in tumor size between visible and non-visible tumors involving transient signal reduction ($p < 0.05$). CNR gradually increased after rapidly decreasing in the perfusion phase.

Conclusion: SH U 555 A enhanced MRI is valuable in limited cases. Evaluation of tumor blood flow employing dynamic MRI with SH U 555 A is affected by tumor size and requires optimal timing of the perfusion phase.

Keywords: *superparamagnetic iron oxide, SH U 555 A, dynamic MRI, hepatocellular carcinoma*

Introduction

It has been reported that the capability of MRI with superparamagnetic iron oxide (abbreviated here as “SPIO”) to detect liver tumors is equal or superior to that of angiographically-assisted CT.¹ However, SPIO-enhanced MRI is associated with one shortcoming: it does not provide information on the blood supply to the tumor. To accomplish this, additional dynamic CT or dynamic MRI with

gadopentetate dimeglumine is required. With hepatocellular carcinomas, it is very important to determine vascularity before settling on a therapeutic course. Diagnostic efficiency improves when information on tumor vascularity becomes available through SPIO-enhanced MRI.

SH U 555 A (Schering, Berlin, Germany), a new SPIO, is coated carbodextran. The hydrodynamic diameter is 62 nm and the diameter is smaller than that of ferumoxide (Feridex®, Tanabe Pharmaceutical, Tokyo, Japan). Unlike ferumoxide, SH U 555 A does not show side effects after rapid intravenous injection.^{2,3} Several studies have been made of the

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possible use of dynamic MRI with SH U 555 A,⁴⁻⁶ but most discussed its quantitative evaluation.^{4,5} In routine clinical practice, quantitative determination is troublesome. Its utility would be much enhanced if a visual evaluation were to become possible. In the late phase II clinical trial of SH U 555 A, recently completed in Japan, the possibility of visual evaluation of the blood flow in cases of hypervascular hepatocellular carcinomas was examined. Although the number of participating patients was very small, significant findings were obtained; these are reported below.

Materials and Methods

The subjects were six patients (five males and one female; mean age, 66 years) who participated in the phase II clinical trial of SH U 555 A between February and May 2001. Written consent was obtained from each patient prior to the trial. All were suffering from type C viral cirrhosis, and an evaluation of the findings from ultrasonography or CT conducted during the clinical course suggested the presence of hepatocellular carcinoma. The diagnosis of hypervascular hepatocellular carcinoma (HCC) was based comprehensively on CT hepatic

arteriography (CTHA) and CT during arterial portography (CTAP). Briefly, hypervascular HCC was defined as a hypervascular lesion seen on CTHA and an area lacking the portal blood flow in CTAP. Pseudolesions were excluded from these lesions.⁷ With this approach, 23 nodules were diagnosed as hypervascular HCC. The maximum diameter observed on the CTHA was used as the tumor diameter, which was 15.0 ± 3.5 mm (mean $\pm$ SD).

CTHA and CTAP were conducted on all patients three days after SH U 555 A administration. CT was performed with a Sufida CT scanner (Shimazu, Kyoto, Japan). For CTHA, a total of 15 ml of ioxilan (Imagenil 300, Kyowa Hakko, Tokyo, Japan) was injected into the common hepatic artery at a rate of 1.5 ml per second; the scan was started five seconds after the start of the injection. Imaging was conducted twice, once for the cephalic half and again for the caudal half. For CTAP, ioxilan was diluted twice and a total of 90 ml was injected into the superior mesenteric artery at a rate of 2 ml per second; the scan was started 30 seconds after the start of the injection. For both CTHA and CTAP, the imaging conditions were: collimation, 5 mm; table speed, 7 mm; reconstruction, 7 mm, and helical scanning.

Fig. 1. Determining the optimal timing for obtaining the perfusion phase (a) Plain T_2^* -weighted image and (b) perfusion phase of the slice depicting the kidney of the patient in Fig. 4. (c) Plain T_2^* -weighted image and (d) perfusion phase of the slice depicting the kidney of the patient in Fig. 2. Compared with (c), (d) exhibits a transient signal reduction of the kidney. This is not apparent when comparing (b) with (a). These findings suggest that the timing of the imaging is not appropriate in the case shown in Fig. 4.

MR imaging was performed with a superconducting scanner operating at 1.5T (Siemens, Erlangen, Germany). For MRI, the T₁-weighted gradient echo and T₂-weighted fast spin echo methods were employed, followed by dynamic MRI. The T₁-weighted plain images were obtained under the following conditions: TR, 165 ms; TE, 4.5 and 6.7 ms; flip angle, 90°; matrix, 179 × 256; field of view (FOV), 35 cm; number of excitation (NEX), 1; acquisition time, 18 s, slice thickness, 8 mm; and gap, 2 mm. The T₂-weighted images were obtained under the following conditions: TR, 4259 ms; TE, 108 ms; echo train length, 29; matrix, 167 × 256; FOV, 35 cm; NEX, 1; acquisition time, 21 s; slice thickness, 8 mm; and gap, 2 mm. Dynamic MRI was conducted for the T₂*-weighted images under the following conditions: TR, 165 ms/TE 9 ms; flip angle, 30°; FOV, 35 cm; matrix, 179 × 256; NEX, 1; slice thickness, 8 mm; slice gap, 2 mm; and imaging time, 18 s. The contrast medium, SH U 555 A, was rapidly injected into a cubital vein and the images were obtained at 10 s and at 1, 2, 3, 4, 5 and 10 min later. For each procedure, the contrast medium was injected forcefully and rapidly into a vein manually, followed by forceful flushing with 20 ml of a physiological saline as rapidly as possible. The dosage of the contrast medium was 8 μmol Fe/kg BW for three patients and 12 μmol Fe/kg BW for three patients. Ten minutes after administration of the contrast medium, the T₂-weighted images were obtained under the conditions defined for the procedure before administration of the contrast medium.

The qualitative evaluation was performed as follows: Dynamic MRI obtained 10 s after contrast medium administration (perfusion phase) was compared with the image obtained before contrast medium administration to determine if a signal reduction could be detected visually. Two radiologists performed visual examinations and made a final determination through consensus. Comparisons of the sizes of visible and non-visible lesions were performed with Welch's t test. P values smaller than 0.05 were considered statistically significant.

For quantitative evaluation, a region of interest (ROI) was established for each phase in which the signal intensity (SI) for the tumor and hepatic parenchyma were determined. For the tumor, the entire lesion was established as the ROI. For the hepatic parenchyma, an area was established that avoided the vasculature. If a lesion were not visible on either unenhanced or enhanced MRI, an ROI of adequate size was situated in the same anatomic location as with the CTHA and CTAP. The ROI

Fig. 2. A 59-year-old male with HCC
(a) Three hypervascular HCCs are seen on CTHA.
(b) The three tumors seen in (a) can also be identified in the T₂*-weighted image obtained 10 min after the start of SH U 555 A administration. (c and d) In the image obtained 10 s after the start of SH U 555 A administration (d), a transient signal reduction (arrowhead) of two tumors is confirmed when compared with plain MRI (c). Transient signal reduction of the small tumors (arrows in a and b) recognized in (a) and (b) at the margin of the liver is not recognized in the perfusion phase.

was always larger than 1 cm². The standard deviations (SD) of background noise were also determined by backtracking in the encoding direction and selecting locations without artifacts. The contrast-to-noise ratio (C/N) was calculated from these findings with the following formula:

$$C/N = (SI \text{ of tumor} - SI \text{ of liver}) / \text{SD of background noise}$$

Results

There were 23 hypervascular HCC detected on CTHA and CTAP. Seventeen of the 23 lesions (74%) were detected on SH U 555 A-enhanced MRI. The size of undetectable lesions on SH U 555 A enhanced MRI was 5.5 ± 1.2 mm and that of detectable lesions was 18.4 ± 14.3 mm. A significant difference was observed between the sizes ($p < 0.05$).

Incorrect timing in acquiring the perfusion phase was suggested from the scarcity of changes in the signals from the kidney (Fig. 1). Two cases with three lesions corresponded to this condition. A lower dosage of SH U 555 A was applied to these two cases. Appropriate timing was suggested in one other case with lower dosage. These three lesions were detectable in the latter phase.

The signal change in the perfusion phase was evaluated in four cases with 14 lesions, excluding the two cases judged as exhibiting inadequate timing for the former reason indicated above. Of 14 lesions detected with SH U 555 A enhanced MRI, transient signal reduction at the perfusion phase was visually recognized in 10 lesions (71%; Figs. 2, 3).

The mean diameter of tumors in which a reduction in signal intensity was visible was 20.8 ± 15.3 mm. The diameter of those tumors without confirmation of signal intensity reduction was 7.8 ± 2.1 mm (Fig. 4). A significant difference between sizes

was shown ($p < 0.05$).

The C/N ratio was evidently reduced during the perfusion phase (Fig. 5). The C/N ratios gradually increased thereafter.

Discussion

Choi et al.¹ reported that SPIO enhanced MRI could be used in place of combing CTHA and CTAP for the preoperative evaluation of patients with HCCs. However, in this study, seven lesions were missed in SPIO-enhanced MRI. All undetectable lesions were smaller than 10 mm. Pauleit et al. reported that the detection of small HCC (≤ 15 mm) in SPIO-enhanced MRI was inferior to that of large HCC.⁸ The following reasons might have contributed to the non-detection of small HCCs in SPIO-enhanced MRI. In cirrhotic liver parenchyma, the accumulation of SPIO particles in Kupffer cells decreases because of the decreasing activity of Kupffer cells.⁹ As a result, a sufficient signal de-

Fig. 3. A 64-year-old male with HCC

(a) CTHA shows hypervascular HCC at liver segment 6. (b) CTAP shows the lesion was a perfusion defect. (c) The tumor seen in (a) and (b) can be identified in the T_2^* -weighted image obtained 10 min after SH U 555 A administration. (d and e) In a comparison of plain MRI (d) and perfusion phase (e), a transient signal reduction of the tumor is recognized (arrow in e). The shape of the lesion in the perfusion phase is similar to that of the lesion in CTAP but not in CTHA.

Fig. 4. A 65-year-old male with HCC
(a) CTHA shows hypervascular HCC at liver segment 5. **(b)** In the T_2^* -weighted image obtained 10 min after SH U 555 A administration, a tumor corresponding to the hypervascular lesion recognized in **(a)** is seen. **(c)** and **(d)** In a comparison of plain MRI **(c)** and the perfusion phase **(d)**, no transient signal reduction of the tumor is recognized.

crease could not be obtained for the liver parenchyma and small lesions became obscure. Another reason was the blooming effect.¹⁰ In the present study, a comparatively long echo time was used in the T_2^* -weighted imaging.

For the imaging sequence of dynamic MRI with SH U 555 A, studies exist in which T_1 -weighted images are employed^{5,6} or T_2^* -weighted images are utilized^{4,5}; however, no consensus has been reached on this subject. In the former, a sufficient T_1 shortening effect could not be obtained^{5,6}; therefore, it was decided that visual detection would be difficult at the current technological level and it was not adopted in the current study. Since the T_2^* -weighted dynamic MRI appeared more promising in view of the results from quantitative evaluations^{4,5} and from a previous study on its visual evaluation,⁴ the current study was based on the T_2^* -weighted images. For the imaging sequences, a choice may be made between the echo planar method (EPI method) in which time resolution was preferred and the non-EPI gradient echo method (GRE method) in which spatial resolution was preferred. The EPI method does not provide sufficient spatial resolution for the abdominal region and was therefore

not selected for the present study. The imaging parameters were determined with a particular focus on the retention of the susceptibility effect, image quality, image acquisition time, and number of images acquired.

When conventional dynamic MRI with gadopentetate dimeglumine was employed, the blood flow in hypervascular HCC was examined in the arterial dominant phase. It was reported that hypervascular HCC is detected at the arterial dominant phase at frequencies of 70% to 90%.¹⁰⁻¹² The detection of blood flow at the perfusion phase of SPIO-dynamic MRI in the current study was not satisfactory. Moreover, most studies on dynamic MRI with gadopentetate dimeglumine were intended to detect tumors with diameters of approximately 1 cm, while the tumors studied here measured 1.5 cm on average. It is suggested that the signal reduction of lesions in the perfusion phase could not be detected due to a slight signal change. Therefore, lesion conspicuity was obscure. It was expected that administration of a higher dosage of SH U 555 A would have a higher susceptibility effect and that the signal reduction of the perfusion phase might improve. In the present study, two dosages were ex-

Fig. 5. Contrast-to-noise ratio of SH U 555 A perfusion imaging

The graph shows the contrast-to-noise ratio in hypervascular hepatocellular carcinoma. (a) and (b) represent groups that did and did not exhibit a visually recognizable signal reduction at the perfusion phase, respectively. In the former group, the transient contrast-to-noise ratio reduction in the perfusion phase was clearer.

aminated, but two of three patients in the lower dosage group exhibited incorrect timing for acquisition the perfusion phase. As a result, the effect of the higher dosage and lower dosage could not be compared. Improving the conspicuity in the perfusion phase is an issue for future studies.

The blood flow could not be evaluated in some cases in this study due to irregularities in the imaging timing. According to a study by Ichikawa, et al.,⁴ the contrast-to-noise ratio is reduced significantly 15 s after intravenous injection of SH U 555A; therefore, in the current study, the imaging for the perfusion phase was started 10 s after the start of injection of the contrast medium. However, a drop in the percentage enhancement ratio of the hypervascular HCC occurs in a very short time (within 10 s)⁴ and it is highly probable that the timing of the imaging will not be correct in those patients with compromised circulatory dynamics

(e.g., as in cardiac insufficiency). Similar problems develop in association with dynamic MRI with gadopentetate dimeglumine, necessitating innovations such as multiple imaging of the artery-dominant phase,^{13,14} combined use of monitoring scan, and projecting the imaging start time by using a test injection of a contrast medium.¹⁵ Even when dynamic MRI with SH U 555A is employed, these innovations might have to be considered in the future.

Several limitations were encountered in this study. One was the lack of histopathological confirmation of the diagnosis of HCC. The combination of CTHA and CTAP revealed high sensitivity and high specificity.^{16,17} Consequently, these modalities were used as the benchmark. Another limitation was the very small number of subjects in the study group, which was attributed to the fact that this study was performed as part of a phase II clinical trial. Further studies are required to address this problem.

Conclusion

Dynamic MRI employing SH U 555 A is a valuable tool for evaluating the vascularity of the lesion in a limited number of cases. Evaluations of tumor blood flow employing dynamic MRI with SH U 555 A are affected by tumor size and the timing of the perfusion phase.

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