Tumor Enhancement Characteristics of New Intravascular Contrast Agent Dendrimers DTPA-D1Glu(OH). Experimantal Study with Hypervascular Hepatocellular Carcinoma of Rats.

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Introduction

Hepatocellular carcinoma (HCC) is relatively rare in the United States; however, it is one of the most common causes of cancer death worldwide. Early diagnosis and treatment contribute to amelioration of consequence. MR diagnosis of HCC has traditionally been made by 3DFT or 2DFT-FSPGR dynamic study with non-specific extravascular and extracellular gadolinium chelates; therefore, high temporal resolution and high performance gradient system has been required for the MR scanners. In this study, with use of conventional spin echo sequence, we have tested if a newly developed intravascular contrast agent, dendrimers DTPA-D1Glu(OH) can increase the contrast of HCC within the cirrhotic liver of a rat model.

Materials and methods

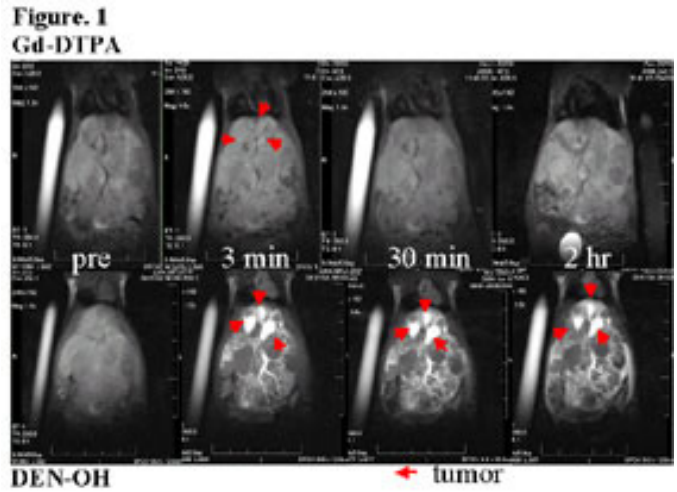
Dendrimers DTPA-D1Glu(OH) functionalized ligand for a lanthanide ion based on dendric architecture was synthesized by our group. Dendritic frameworks were applied as a paramagnetic metal support. These ligands are composed of diethylenetriaminepentaacetic acid (DTPA) and glycodendrimers. The molecular weight of the contrast agent is 1448.45D. Male F344 rats (SLC., Co. Ltd. Shizuoka, Japan) (5 weeks, 80g BW) were given distilled water containing 100ppm diethylnitrosamine for 11 weeks to induce liver cancers. HCCs and dysplastic nodules of various degrees were induced in the liver of the rats. The HCCs induced in this model were extremely hypervascular. Three tumor bearing F344 rats were used for the contrast enhanced MRI and histopathological analysis. All rats were examined with two contrast media consecutively (i.e.: Gd-DTPA (0.10 mmol/kg, Magnevist, Nihon Schering, Osaka, Japan) first and more than 6 hours later dendrimers DTPA-D1Glu(OH) (0.05 mmol/kg) was given). A 3.0T imager (Magnetom Allegra, Siemens Medical Systems) together with a home made surface coil was used for the imaging. Under general anesthesia induced by an intraperitoneal injection of pentobarbital (50 mg/kg), T1-weighted conventional spin-echo images and T2-weighted fast spin-echo images were acquired before contrast administration. T1-weighted spin-echo imaging was repeated at 3 min, 30 min, 1 hr, and 2hr after contrast administration. The parameters used for T1-weighted imaging were: TR/TE = 250/9.1 ms, image matrix = 256 × 192, slice thickness = 3 mm, and slice gap = 0.9 mm. For T2-weighted imaging, the parameters were TR/TE = 2000/86 ms, image matrix = 256 × 128, slice thickness = 2 mm, and slice gap = 0.6 mm. After completion of image acquisition, the rats were sacrificed and the livers were excised from the rats and fixed in the 10% formaldehyde solution. The livers were then sliced identically to the axial planes for MR images. The axial histological sections were stained with hematoxylin and eosin (H-E) for microscopic investigations, and the nodules were correlated with MR images. The histological sections were correlated with MR images and the HCCs more than 5 mm in diameter were numbered. Mean signal intensities and standard deviations (SD) were measured by focusing circular regions of interest on the tumor, the liver and the back ground. The contrast to noise ratios (CNR) were then calculated for each HCCs. All data were presented as mean ± standard deviations (SD). Differences between CNR values obtained before and after administration of contrast material within each group were evaluated with a repeated-measure analysis of variance (ANOVA) followed by Fisher's protected least significant difference (PLSD) test. The statistically significant difference between contrast groups was tested with paired t-test, where Bartlett's test indicated homogeneity of variance, or by a non-parametric Mann-Whitney test for significantly different variances.

Results

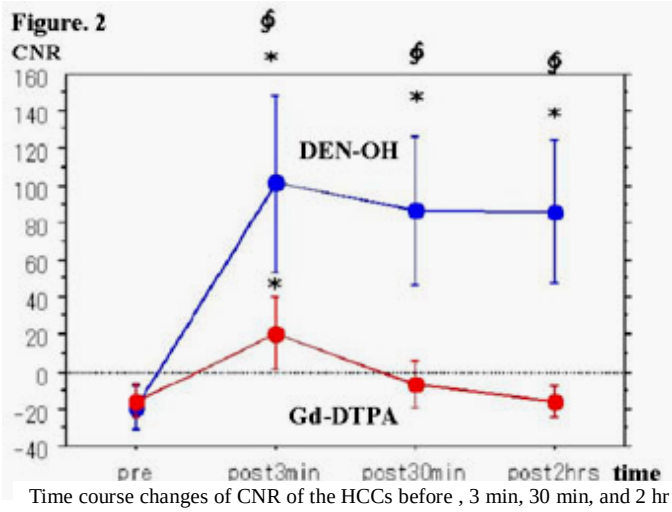
A total of 23 hypervascular HCCs were induced in the 3 rats. Representative MR images obtained before and 3 min, 30 min, and 2 hr after injection of Gd-DTPA and dendrimers DTPA-D1Glu(OH) are shown in Figure 1. HCCs were clearly identified as extremely enhanced tumors with use of T1 weighted conventional spin echo sequence after administration of dendrimers DTPA-D1Glu(OH); however, Gd-DTPA depicted HCCs less clearly. Figure 2 shows the time course changes of CNR of the HCCs before and after the injection of Gd-DTPA and dendrimers DTPA-D1Glu(OH). CNR of HCCs reached peak 3 minutes after contrast administration in both cases. In Gd-DTPA injection, CNR of the HCCs decreased promptly; however, dendrimers DTPA-D1Glu(OH) revealed more potent and sustained contrast enhancement of the HCCs up to 2 hours after contrast injection.

Conclusion

New blood pool agent dendrimers DTPA-D1Glu(OH) has a potential to depict hypervascular HCCs even with conventional spin-echo sequence owing to its broad imaging windows and potent and sustained enhancement as compared with Gd-DTPA.



Representative MR images obtained before, 3 min, 30 min, and 2 hr after injection of Gd-DTPA (upper row) and dendrimers DTPA-D1Glu(OH) (lower row).
Note stronger and sustained enhancement of HCCs after injection of dendrimers DTPA-D1Glu(OH).



Time course changes of CNR of the HCCs before , 3 min, 30 min, and 2 hr after the injection of Gd-DTPA and dendrimers DTPA-D1Glu(OH) (DEN-OH). Blue line shows the time course changes of demdrimers DTPA-D1Glu(OH), and red line shows that of Gd-DTPA.
Error bar : standard deviations (SD).