MRI Contrast Agents in Malignant Fibrous Histiocytoma (MFH) for Gadolinium Neutron Capture Therapy (Gd-NCT)

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Introduction: Neutron-capture therapy (NCT) is a malignant tumor therapy that exploits the nuclear neutron capture reaction of radiation-producing agents. NCT with several elements was first postulated by Locher in 1936 [1]. The most common element for NCT is boron (B-NCT), and the clinical outcome with the use of B-NCT has been good in patients with malignant melanoma [2]. Nonetheless, other more effective radiation-producing elements for NCT are still required. Gadolinium is also a radiation-producing element that provides the neutron capture reaction by thermal neutron irradiation. NCT with gadolinium (Gd-NCT) has several advantages over B-NCT. Not only does gadolinium have the highest thermal neutron capture cross-section (66 times larger than that of boron), but it has also been used as a diagnostic agent in enhanced magnetic resonance imaging (MRI) examinations and shows promise in future Gd-NCT therapy under enhanced MRI diagnosis. Although the therapeutic potential of Gd-NCT has been explored in recent years, there is no study on therapy applied to musculoskeletal tumors such as sarcoma. Consequently, we conducted this study using a sarcoma cell line, malignant fibrous histiocytoma (MFH) Nara-H. First, we investigated whether the accumulation of gadolinium in the cells could be detected by the MRI system. We used both the commercially available MRI contrast (Gd-DTPA) and the biodegradable and highly gadopentetic acid (Gd-DTPA)-loaded chitosan nanoparticles (Gd-nanoCPs) prepared by a novel emulsion-droplet coalescence technique.

Materials and Methods: Human sarcoma cell line malignant fibrous histiocytoma (MFH) (Nara-H) was cultured in Eagle MEM supplemented with antibiotic-antimycotic solution and FBS and incubated in a humidified atmosphere with 5% CO2 at 37 degree C. An adequate number of cells produced in the initial culture were harvested and re-seeded in three 150 cm^2 cell-culture flasks at a density of 10000 cells/flask. When the culture reached 70% confluence, the culture medium was aspirated. The first flask was used as the control and incubated with fresh culture medium for 12 hrs. The second and third flasks were incubated for 12 hrs with Gd-DTPA and Gd-nanoCPs suspension, respectively, in fresh culture medium with Gd at a concentration of 450 μg/m in a humidified atmosphere with 5% CO2 at 37 degree C. The culture medium of the three flasks was then aspirated, and the cells were washed twice with PBS to remove free Gd and Gd-nanoCPs and collected into three falcon tubes by detachment with 0.25% trypsin and centrifuged. The supernatant was discarded and the cells were gently washed with PBS and centrifuged again. The pellet was collected and the supernatant was discarded. The three falcon tubes were then set into the 3-tesra MRI system to obtain signal intensities from each pellet. R, Control; M, Gd-DTPA; G, Gd-nanoCPs (Table 1). In contrast, and compared with the control, Gd-DTPA was more effective than Gd-nanoCPs in reducing T1 (Table 1). The higher numerical reduction of T1 implies that the enhancement effect on tissue was higher on enhanced MRI examination. This contrast suggested that the larger accumulation exerted the adverse effect of lowering the enhancement of MRI. Future studies are warranted to gain insight into the therapeutic potential for Gd-NCT.

Results: The MRI image was successfully acquired from the three pellets (Fig. 1b). The data of each specimen (cell, Gd-nanoCPs, Gd-DTPA) plotted on a graph (Fig. 2) showed a linear relation, and T1 as measured from the graph was 630, 400, and 227, respectively. The amount of gadolinium in Gd-nanoCPs and Gd-DTPA measured by ICP-AES was 30.5 μg, 9.5 μg, respectively (Table 1). In contrast, and compared with the control, Gd-DTPA was more effective than Gd-nanoCPs in reducing T1 (Table 1). The higher numerical reduction of T1 implies that the enhancement effect on tissue was higher on enhanced MRI examination. This contrast suggested that the larger accumulation exerted the adverse effect of lowering the enhancement of MRI. Future studies are warranted to gain insight into the therapeutic potential for Gd-NCT.

Discussion: Neutron-capture therapy with gadolinium (Gd-NCT) has therapeutic potential, especially that gadolinium is generally used as a contrast medium in magnetic resonance imaging (MRI). Thus, both diagnosis and treatment can be carried out simultaneously. Future success of clinical Gd-NCT trials will depend on both the visualization of tumor cells on enhanced MRI and the selective large accumulation of gadolinium compounds in individual tumor cells, conditions that Gd-nanoCPs satisfy. Our results showed that both Gd-DTPA and Gd-nanoCPs accumulated in sarcoma cells. Furthermore, the accumulation of gadolinium in cells treated with Gd-nanoCPs was larger than that in cells treated with Gd-DTPA.