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Original article

Magnetic resonance imaging of osteosarcoma using a bis(alendronate)-based bone-targeted contrast agent

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ABSTRACT

Magnetic resonance (MR) is currently used for diagnosis of osteosarcoma but not well even though contrast agents are administered. Here, we report a novel bone-targeted MR imaging contrast agent, Gd_2-diethylenetriaminepentaacetate-bis(alendronate) (Gd_2-DTPA-BA) for the diagnosis of osteosarcoma. It is the conjugate of a bone cell-seeking molecule (i.e., alendronate) and an MR imaging contrast agent (i.e., Gd-DTPA). Its physicochemical parameters were measured, including pK_a, complex constant, and T_1 relaxivity. Its bone cell-seeking ability was evaluated by measuring its adsorption on hydroxyapatite. Hemolysis was investigated. MR imaging and biodistribution of Gd_2-DTPA-BA and Gd-DTPA were studied on healthy and osteosarcoma-bearing nude mice. Gd_2-DTPA-BA showed high adsorption on hydroxyapatite, the high MR relaxivity (r_1) of 7.613 mM^{-1} s^{-1} (2.6 folds of Gd-DTPA), and no hemolysis. The MR contrast effect of Gd_2-DTPA-BA was much higher than that of Gd-DTPA after intravenous injection to the mice. More importantly, the MR imaging of osteosarcoma was significantly improved by Gd_2-DTPA-BA. The signal intensity of Gd_2-DTPA-BA reached 120.3% at 50 min, equal to three folds of Gd-DTPA. The bone targeting index (bone/blood) of Gd_2-DTPA-BA in the osteosarcoma-bearing mice was very high to 130 at 180 min. Furthermore, the contrast enhancement could also be found in the lung due to metastasis of osteosarcoma. Gd_2-DTPA-BA plays a promising role in the diagnoses of osteosacomas, including the primary bone tumors and metastases.

1. Introduction

Osteosarcoma is a serious disease and the most common type of bone cancers. It is the second leading cause of cancer-related deaths in the children and young adults. Osteosarcoma has a high metastatic rate of about 20%. The lung and other bones are the most common targets [1,2]. Current osteosarcoma therapies include surgical resection and chemotherapy. However, osteosarcoma frequently develops resistance to conventional chemotherapies and tumor recurrence. Amputation of the affected limbs is often the only option but even this usually fails to save a patient's life due to early metastases [3]. Therefore, the early diagnosis of osteosarcomas and the possible metastases are very important to initiate the treatment of this serious disease as soon as possible.

Magnetic resonance (MR) imaging is a most commonly used diagnostic technique of diseases with a non-invasive way [4]. Non-enhanced MR imaging (MRI) may not discriminate the tumor (e.g., osteosarcoma) and the surrounding healthy tissues due to the low signal contrast ratio between adjacent tissues [5]. MR bioimaging probes (contrast agents) appeared in 1988. They can shorten the relaxation time of the nearby water molecules to enhance the contrast between tissues, and be widely applied for angiography and perfusion imaging [6,7]. Magnevist®, an MRI contrast agent, i.e., gadolinium diethylenetriaminepentaacetate (Gd-DTPA), has been clinically applied for many years in spite of its low relaxation, high dose, and no tissue targeting.

Here, we report a novel MRI contrast agent with enhanced relaxation and bone targeting for the diagnosis of osteosarcoma. It is the conjugate of Gd-DTPA and alendronate (a clinically applied bone-targeted agent for therapy of osteoclastogenesis). The

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contrast agent, Gd_2-diethylenetriaminepentaacetate-bis(alendronate) (Gd_2-DTPA-BA, Fig. 1), was synthesized, characterized, evaluated *in vitro* and *in vivo* on the osteosarcoma-bearing animal models in comparison with Gd-DTPA.

2. Materials and methods

2.1. Materials

Magnevist®, i.e., Gd-DTPA, was purchased from Bayer HealthCare Pharmaceuticals Inc. Organic solvents were of analytical grade and other chemicals were of reagent grade. Purified water was prepared with the Heal Force Super NW water system (Shanghai Canrex Analytic Instrument Co., Ltd., China). Hydroxyapatite was purchased from Aladin Industrial Corporation, Shanghai, China. Osteosarcoma cell UMR-106 was provided by Puhe Medical Company, Jiangsu, China. Ultraviolet–visible (UV–vis) spectra, infrared (IR) spectra, and nuclear magnetic resonance (NMR) spectra were recorded on a Purkinje TU-1901 spectrophotometer (Beijing Purkinje General Instrument Co., Ltd., Beijing, China), a Bio-Rad FTS-65A infrared ray spectrometer, and a JNM-ECA-400 NMR spectrometer, respectively.

2.2. Animals

Balb/C nude mice were from the Laboratory Animal Center of Beijing Institute of Radiation Medicine (BIRM) were used. The handling and surgical procedures of animals were conducted strictly according to the Guiding Principles for the Use of Laboratory Animals. All of the studies were conducted in accordance with the National Institutes of Health guide for the care and use of Laboratory animals. The animal experiments were approved by the Animal Care Committee of BIRM.

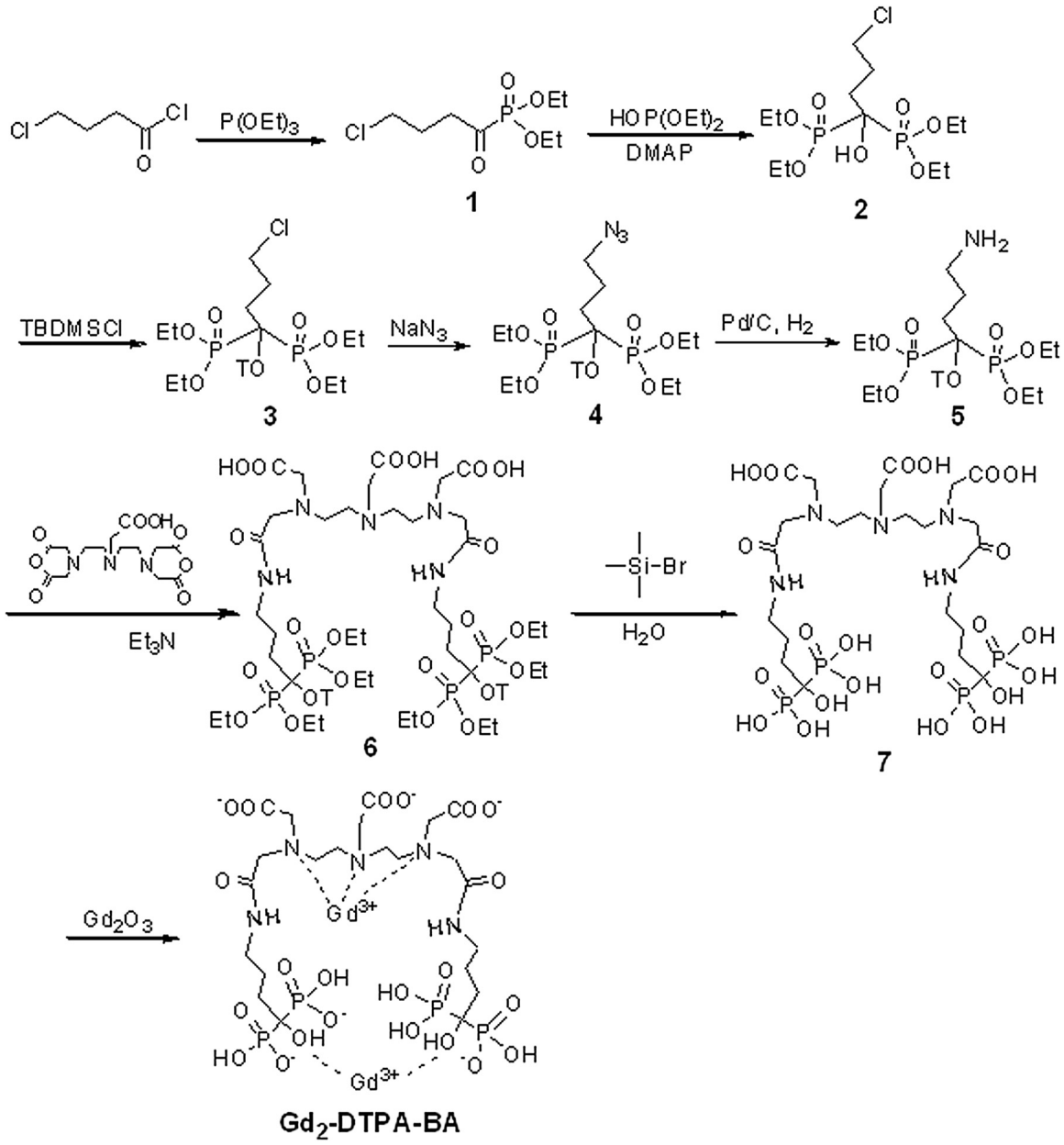

Fig. 1. Synthetic route of Gd_2-DTPA-BA.