Proton and sodium MRI follow-up of human colorectal tumors implanted in mice. Comparison between two photodynamic therapy protocols.

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Introduction: Photodynamic therapy is an established cancer treatment in which a non-mutagen photosensitizing (PS) agent is activated by exposure to visible light. Absorption of light initiates the photochemical reactions leading to the generation of cytotoxic products (reactive oxygen species - ROS) responsible for the therapeutic effects. Vasculature damage and necrosis or apoptosis decrease cell density and increase the local sodium concentration [1]. Since sodium magnetic resonance imaging (23Na MRI) directly monitors variations of sodium concentrations in a non-invasive way, it can be used to follow-up the tumor response to therapy from the very beginning and throughout the treatment [2].

Methods MRI: 1H and 23Na MRI were performed at 4.7 T using a Bruker Biospec small animal MRI scanner. The MRI probehead consists of a double tuned volume resonator (birdcage) used for transmitting / receiving 1H signals and transmitter 23Na r.f. channel, and a surface coil nested inside the birdcage for receiving 23Na signals. Multi-slice, multi-echo 1H images were recorded for localization purposes, (respiratory trigger, FOV=6.8cm, TE=12ms, NE=10, matrix 256x256, slice thickness 1mm) and tumor volume determination. Single-slice, multi-echo (NE=28) 23Na images were recorded for sodium studies, (respiratory trigger, TE=6.7ms, FOV=6.8cm, matrix 64x64, slice thickness 3mm) using 160 averages. The sodium resolution was (1x1x3) mm³ and the acquisition time was 75 min. This sequence allowed us to image mainly the extracellular tumor compartment. Treatment protocol: Flank implanted nude mice with human colorectal tumors were used. Since the damage induced by PDT is strictly related to PS localization during illumination, two regimens were devised for this study. Mice treated with a single-dose, anti-vascular regimen received one i.v. injection of PS (0.6 mg/kg polyethylene glycol 400/ethanol/physiological serum: 3/2/5 per volume) followed 10 min later by exposure to red light (650 nm). Conversely, the second PDT protocol, which targeted both cancer cells and blood vessels was initiated localized. Histological analysis confirmed the presence of necrosis and/or new vessels have been formed (Fig.2 A,B,C). Anyhow the blood vessels positioned beyond the red light penetration depth were not damaged by the treatment and continued the nutritional supply. Two hours after the PS activation in the second treatment protocol a moon-crescent shaped region with high sodium signal appeared on an average depth compatible with the red light penetration into the tissue (4-5 mm at 650 nm) (Fig.2E). 24 h after the PS activation the 1H image showed an increase of the tumor volume possibly due to inflammatory edema that often accompanies PDT treatment. The 23Na image (Fig.2F) showed widespread high sodium concentration in the tumor slice indicating an increase of the extracellular space. This change in sodium signal suggests that a massive process of necrosis and/or apoptosis was taking place in a much larger area than the moon-crescent shaped region where ROS damage was initially localized. Histological analysis confirmed the presence of necrosis.

Conclusions: A single-dose antivascular-PDT does not prevent the tumoral growth. Conversely, the second PDT protocol, which targets both blood vessel and tumor cells, led to important damage of the tumor architecture. Our work indicates that in vivo dual 1H and 23Na MRI is a non-invasive technique well suited for both longitudinal follow up and early treatment assessment. We could easily follow the transition from low sodium signal before treatment to high sodium signal characteristic of damaged areas without adding any exogenous contrast agent.


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