Study of Gd-based MR contrast agents encapsulated in the phosphatidylglycerol-glycerol-based thermosensitive liposomes for improved MR-guided chemothermotherapy

T. Wang1,2, M. Hossann1,2, M. Peller3, M. Reiser3, R. D. Issels1,2, and L. H. Lindner1,2
1Department of Internal Medicine III, University Hospital, Grosshadern, Munich, Bavaria, Germany, 2CCG Hyperthermia, Institute of Molecular Immunology, Helmholtz Center Munich – German Research Center for Environmental Health, Munich, Bavaria, Germany, 3Department of Clinical Radiology, University Hospital, Grosshadern, Munich, Bavaria, Germany

Introduction: Recently, a new formulation based on phosphatidylglycerol-glycerol (DPPGOG) of thermosensitive liposomes (TSL) with encapsulated 1H MR T1 contrast agent (CA) gadodiamide has been designed [1] and characterized in vitro and in vivo [2,3] for noninvasive MR temperature monitoring during chemotherapy combined with hyperthermia in patients with soft tissue sarcomas. The encapsulated gadodiamide is released around the gel-to-liquid crystalline phase transition temperature of phospholipid membrane and leads to the MR signal intensity change due to T1 shortening. In this work, four representative Gd-based T1 CAs with diverse chemical structures were separately encapsulated in the DPPGOG-TSL and studied by measuring the dependence of their T1 on temperature while heated from 30 to 50 °C to explore their potential for the optimal T1 enhancement effect.

Materials and Methods: Linear nonionic Gd-DTPA-BMA (Omniscan™, GE, USA), linear ionic Gd-DTPA (Magnevist®, Bayer, Germany), macrocyclic nonionic Gd-BT-DO3A (Gadovist®, Bayer, Germany), and macrocyclic ionic Gd-DOTA (Dotarem®, Guerbet, France) were previously diluted to 323 mOs kg⁻¹ with water from the stock solutions and yielded a final concentration of 250, 81, 202, and 115 mM, respectively, under consideration of their different osmolalities [4]. The DPPGOG-TSL with these CAs were then prepared separately by successive lipid film hydration, extrusion, and dialysis [2]. A sample of the DPPGOG-TSL with each CA was incubated for 10 minutes at the desired temperature in order to reach the thermal equilibrium while heated from 30 to 46 °C in steps of 2 °C and the T1 ± standard deviation was acquired once. All T1 measurements were performed on a 0.47 T-NMR-Analyzer (Minispec NMS120, Bruker, Germany) and by using the inversion recovery technique in combination with a water bath and a thermostat.

Results: In Figure 1, from 30 to 38 °C, water exchange between the DPPGOG-TSL interior and exterior increased with the exception of negligible CA release from the DPPGOG-TSL, resulting in the slight T1 decreases. The release began at approximately 37.6 °C and ended at 43.4 °C, resulting in the drastic T1 decreases. Above 43 °C, all encapsulated CAs were completely released and T1 changes were not more obvious. Table 1 summarized T1 values at 37.6 °C and 43.4 °C as well as the corresponding percent T1 decreases (ΔT1%). The DPPGOG-TSL with encapsulated macrocyclic nonionic Gadovist® and linear nonionic Omniscan™ showed strong ΔT1% of -67% and -64%, respectively. In comparison, those with encapsulated macrocyclic ionic Dotarem® and linear ionic Magnevist® showed weak ΔT1% of -40% and -14%, respectively.

Conclusions: These preliminary results showed that Gd-based CAs with nonionic chemical structure seem to be more suitable than that with ionic structure and additionally one with macrocyclic structure is better than that with linear structure for the optimal application of DPPGOG-TSL to noninvasive MR thermometry during tumor treatment using chemotherapy combined with hyperthermia.