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Surrogate MRI markers for hyperthermia-induced release of doxorubicin from thermosensitive liposomes in tumors

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Abstract

The efficacy of systemically applied, classical anti-cancer drugs is limited by insufficient selectivity to the tumor and the applicable dose is limited by side effects. Efficacy could be further improved by targeting of the drug to the tumor. Using thermosensitive liposomes (TSL) as a drug carrier, targeting is achieved by control of temperature in the target volume. In such an approach, effective local hyperthermia (40-42°C) (HT) of the tumor is considered essential but technically challenging. Thus, visualization of local heating and drug release using TSL is considered an important tool for further improvement. Visualization and feasibility of chemodosimetry by magnetic resonance imaging (MRI) has previously been demonstrated using TSL encapsulating both, contrast agent and doxorubicin (DOX) in the same TSL. Dosimetry has been facilitated using T_1-relaxation time change as a surrogate marker for DOX deposition in the tumor. To allow higher loading of the TSL and to simplify clinical development of new TSL formulations a new approach using a mixture of TSL either loaded with DOX or MRI contrast agent (CA) is suggested. This was successfully tested using phosphatidyldiglycerol-based TSL ($DPPG_2$-TSL) in Brown Norway rats with syngeneic fibrosarcomas (BN175) implanted at both hind legs. After intravenous application of DOX-TSL and CA-TSL, heating of one tumor above 40°C for 1 h using laser light resulted in highly selective DOX uptake. The DOX-concentration in the heated tumor tissue compared to the non-heated tumor showed an almost 10-fold increase. T_1 and additional MRI surrogate parameters such as signal phase change were correlated to intratumoral DOX concentration. Visualization of DOX delivery in the sense of a chemodosimetry was demonstrated. Although phase-based MR-thermometry was affected by CA-TSL, phase information was found suitable for DOX concentration assessment. Local differences of DOX concentration in the tumors indicated the need for visualization of drug release for further improvement of targeting.

Chemical compounds studied in this article: doxorubicin hydrochloride (PubChem CID 443939), DPPC (PubChem CID 452110), DSPC (PubChem CID 94190), $DPPG_2$ (no PubChem CID available), gadodiamide (PubChem CID 153921)