Targeted Drug Delivery via HIFU and Low-Temperature Sensitive Liposomes

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Studies have shown synergistic effects between hyperthermia and the chemotherapy. Clinical trials in image-guided drug delivery combine high-temperature thermal therapy with chemotherapy agents released in the heating zone via low temperature sensitive liposomes (LTSL). LTSL can release their content within seconds upon heating above ~40 °C. Therefore, LTSL combined with locally applied heat can increase drug concentration at the target region, and reduce systemic tissue exposure.

A spatial and time dependent multi-compartment model was developed to describe the release of DOX from LTSL upon heating, using high intensity focused ultrasound (HIFU) in humans. To reach a larger area of elevated drug concentration, four different focal spots (~16 mm diameter), arranged in a square at 25 mm distance from each were heated sequentially. Three different heating regimen were compared, where each focal spot was heated for 30 s, 1 min, or 2 min with a maximum temperature of 50 °C. Transvascular transport of bioavailable and liposomal DOX, as well as diffusion within the extravascular extracellular space and cell uptake of free DOX were modeled. Additionally DOX concentration was modeled in systemic plasma and normal tissue compartment. Liposomal drug was administered as bolus injection with a dose of 0.7 mg/kg.

Maximum average tumor tissue concentration was calculated in an area of ~50 x 50 mm. For 30 s heating periods, average tumor tissue concentration reached 3.3 ug/g at 1.3 h after HIFU. For 1 min and 2 min heating periods, average tumor tissue concentrations were 3.9 ug/g and 4.7 ug/g, respectively. Peak systemic plasma DOX concentration was in all cases 4.9 ug/g at 29s after bolus administration.

HIFU in combination with LTSL allows localized delivery of drugs with considerably higher local concentrations compared to standard chemotherapy. Computer models may facilitate optimization of drug delivery and heating regimen to maximize local tissue concentration.