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Exploiting the Tumour Microenvironment in Order to Optimise Sonodynamic Therapy for Cancer

Authors : Maryam Mohammad Hadi, Heather Nesbitt, Hamzah Masood, Hashim Ahmed, Mark Emberton, John Callan, Alexander MacRobert, Anthony McHale, Nikolitsa Nomikou

Abstract : Sonodynamic therapy (SDT) utilises ultrasound in combination with sensitizers, such as porphyrins, for the production of cytotoxic reactive oxygen species (ROS) and the confined ablation of tumours. Ultrasound can be applied locally, and the acoustic waves, at frequencies between 0.5-2 MHz, are transmitted efficiently through tissue. SDT does not require highly toxic agents, and the cytotoxic effect only occurs upon ultrasound exposure at the site of the lesion. Therefore, this approach is not associated with adverse side effects. Further highlighting the benefits of SDT, no cancer cell population has shown resistance to therapy-triggered ROS production or their cytotoxic effects. This is particularly important, given the as yet unresolved issues of radiation and chemo-resistance, to the authors' best knowledge. Another potential future benefit of this approach – considering its non-thermal mechanism of action – is its possible role as an adjuvant to immunotherapy. Substantial pre-clinical studies have demonstrated the efficacy and targeting capability of this therapeutic approach. However, SDT has yet to be fully characterised and appropriately exploited for the treatment of cancer. In this study, a formulation based on multistimulus-responsive sensitizer-containing nanoparticles that can accumulate in advanced prostate tumours and increase the therapeutic efficacy of SDT has been developed. The formulation is based on a polyglutamate-tyrosine (PGATyr) co-polymer carrying hematoporphyrin. The efficacy of SDT in this study was demonstrated using prostate cancer as the translational exemplar. The formulation was designed to respond to the microenvironment of advanced prostate tumours, such as the overexpression of the proteolytic enzymes, cathepsin-B and prostate-specific membrane antigen (PSMA), that can degrade the nanoparticles, reduce their size, improving both diffusions throughout the tumour mass and cellular uptake. The therapeutic modality was initially tested in vitro using LNCaP and PC3 cells as target cell lines. The SDT efficacy was also examined in vivo, using male SCID mice bearing LNCaP subcutaneous tumours. We have demonstrated that the PGATyr co-polymer is digested by cathepsin B and that digestion of the formulation by cathepsin-B, at tumour-mimicking conditions (acidic pH), leads to decreased nanoparticle size and subsequent increased cellular uptake. Sonodynamic treatment, at both normoxic and hypoxic conditions, demonstrated ultrasound-induced cytotoxic effects only for the nanoparticle-treated prostate cancer cells, while the toxicity of the formulation in the absence of ultrasound was minimal. Our in vivo studies in immunodeficient mice, using the hematoporphyrin-containing PGATyr nanoparticles for SDT, showed a 50% decrease in LNCaP tumour volumes within 24h, following IV administration of a single dose. No adverse effects were recorded, and body weight was stable. The results described in this study clearly demonstrate the promise of SDT to revolutionize cancer treatment. It emphasizes the potential of this therapeutic modality as a fist line treatment or in combination treatment for the elimination or downstaging of difficult to treat cancers, such as prostate, pancreatic, and advanced colorectal cancer.

Keywords : sonodynamic therapy, nanoparticles, tumour ablation, ultrasound
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