ADJUNCTIVE TUMOUR TREATMENT

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Purpose: Radionuclides have shown to be effective in tumour therapy. However, the side effects determine the maximum deliverable dose. Recently, it has been demonstrated that cells can be permeabilised through sonoporation using ultrasound and contrast microbubbles. The use of sonoporation in treatment of tumours may increase the anti-tumour efficacy of radionuclide treatment. The mechanisms as well as the effects sonoporation in tumour treatment strategies are still not understood. The purpose of this study is to determine the effects of ultrasound and contrast microbubbles on the internalisation of the radionuclide $^{111}$In-DOTA-Tyr³-octreotide in tumour cells. For that purpose we investigated the uptake by tumour cells at different ultrasound setting.

Method: 1] To find the optimal ultrasound settings for ultrasound adjunctive tumour therapy we incubated Rat-pancreatic CA20948 tumour cells with two dyes (MW 40 and 70 KDa) and the uptake levels were compared with cells treated with ultrasound and contrast microbubbles. Ultrasound settings were varied in terms of duty cycle, and total treatment time. Lipid-shelled microbubbles at different concentrations were used. Acoustic frequency (1 MHz), acoustic pressure (MI 0.42), contrast agent (lipid-shelled) and temperature (37°C) were constant. 2] The estimated optimal settings were then used whereby Rat-pancreatic CA20948 tumour cells were incubated with $^{111}$In-DOTA-Tyr³-octreotide.

Results: 1] The highest molecular uptake was found with addition of contrast microbubbles (ratio of 10 bubbles to 1 cell) and with the ultrasound setting: duty cycle 0.0013, MI 0.42, and treatment times of 30 and 60 minutes. 2] These settings were used to enhance the internalisation of $^{111}$In-DOTA-Tyr³-octreotide. For 30 minutes incubation, the internalisation of $^{111}$In-DOTA-Tyr³-octreotide increased by 65% when adjunctive treatment with ultrasound and contrast microbubbles was used compared to control (only $^{111}$In-DOTA-Tyr³-octreotide) (figure 1).
**Figure 1:** US and bubbles enhanced radionuclide internalisation in rat pancreatic tumour cells in vitro.

**Conclusions:** These results demonstrate the feasibility of adjunctive tumour treatment with the radionuclide $^{111}$In-DOTA-Tyr$^3$-octreotate and ultrasound contrast micro bubbles. When using adjunctive ultrasound contrast micro bubble treatment, a lower radionuclide doses are required to reach the same anti-tumour effect.

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