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Ultrasound and microbubble enhanced therapy of orthotopic human pancreatic cancer in mice.

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Abstract

Background and Aim: Adenocarcinoma of the pancreas remains one of the most lethal human cancers as surgery is rarely feasible and chemotherapy produces minimal response(1-3). The viability after being diagnosed with inoperable pancreatic cancer is very low; typical mortality rates of 50% are expected within 3 months of diagnosis (4). In this study we explore the effect of sonoporation (5-8), the formation of transient pores in the cell membrane due to ultrasound or ultrasound and microbubbles, for increased targeted drug delivery of gemcitabine in an orthotopic xenograft model of pancreatic cancer.

Procedure: Clinically safe acoustic conditions were used with treatment times of 10 minutes to ensure no secondary effects due to heating or cavitation. SonoVue was

used as the clinically approved microbubble. Primary tumour development was measured using 3D ultrasound and bioluminescence.

Results: Following just two treatments combining sonoporation and gemcitabine primary tumour volumes were significantly smaller than control groups. Additional therapy dramatically retarded primary tumour growth throughout the course of the disease (Figure 1). A median survival increases of up to 10% were seen demonstrated with respect to control groups with hepatic metastasis determined the primary cause of death.

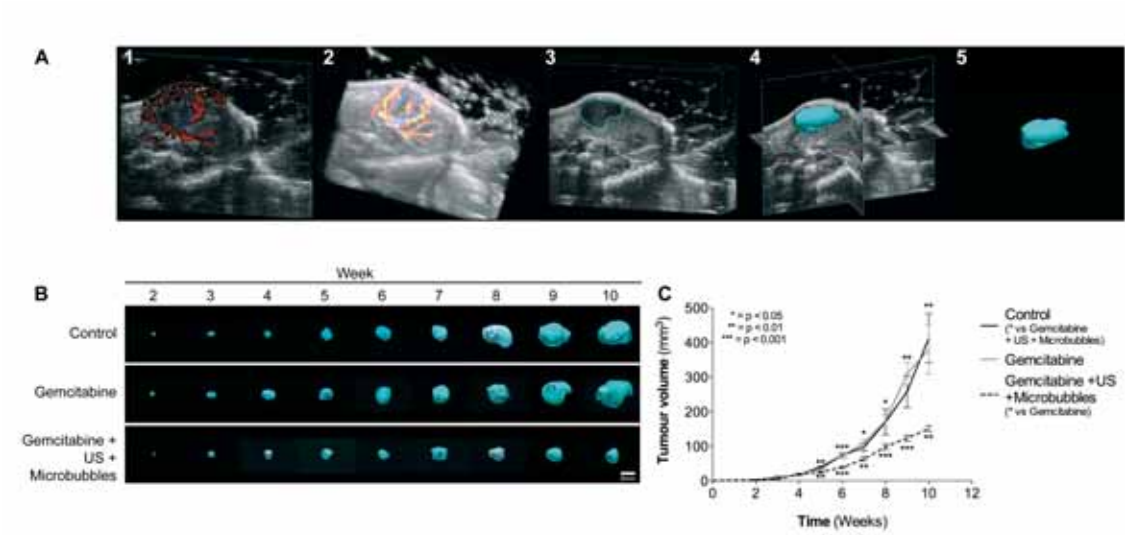

Figure 1: Primary pancreatic tumour volume measured by 3D ultrasound of MIA PaCa-2^{luc} model treated with gemcitabine; gemcitabine microbubbles and ultrasound or control once a week. Panel A shows how the primary tumour was detected and 3D volume was measured. Using colour Doppler the feeding arteries of the tumour and kidney can be easily distinguished in both 2D and 3D (Panel A1 & A2 respectively). The primary tumour can then be manually contoured throughout the 3D stack (Panel A3). The primary tumour can then be visualised within the 3D ultrasound image (Panel A4) or on its own (Panel A5). 3D tumour volume over time can be visualised and compared. The 3D volumes are visualised in Panel B and mean volume ±SEM are shown in Panel C. After two treatments a statistically significant difference can be seen between the combined treatment group and the gemcitabine alone and/or control group.

Conclusion: Combined sonoporation and gemcitabine therapy significantly impedes primary tumour development in an orthotopic xenograft model of human pancreatic cancer, suggesting additional clinical benefits for patients treated with Gemcitabine.

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Notes: