Drs. Bouakaz and Escoffre will present their collaborative research project with Prof. Lecomte.

Nab-paclitaxel delivery with microbubble-assisted ultrasound in human pancreatic cancer mouse model

Rationale and aim – The combination of microbubbles (MBs) and ultrasound is an emerging method for non-invasive and targeted enhancement of anticancer drugs uptake. This method showed to increase local drug extravasation in tumor tissue while reducing the systemic adverse side effects in various tumor models. The present study aims into evaluating the therapeutic efficacy of 2 types of microbubbles both in-vitro and in-vivo for Nab-paclitaxel delivery in a pancreatic tumor model.

Material & Methods – In-vitro, a suspension of human pancreatic cancer BxPC3 cells was exposed to ultrasound (1 MHz, 100 s PRP, 40% DC, 400 kPa, 30s) in presence of QA3216 microbubbles or BR38©
with a ratio of 5:1 MBs/cell. Nab-paclitaxel was injected at a concentration of 2.5 ng/mL. Seventy-two hours later, MTT assay was performed to assess cell viability. In-vivo, BxPC3 tumors were induced by a subcutaneous injection of 5106 cells in both flanks of male nude mouse. When the tumor was significantly perfused, the treatment was initiated as follows: an i.v. administration of Nab-paclitaxel (5 or 20 mg/kg) followed by an i.v. administration of MBs (70 L). Ultrasound insonation as applied using a single-element transducer at 1 MHz (100 s PRP, 40% DC, 400 kPa, 3 mins). The therapeutic efficacy was determined by monitoring the tumor growth using ultrasound imaging. Quality of life of the animals was also assessed.

**Results - In-vitro Nab-paclitaxel delivery** - The exposure of BxPC-3 cells to ultrasound at 400 kPa in presence of BR38® and QA3216 MBs did not modify the cell viability in comparison to the control condition. When the BxPC-3 cells were treated with 2.5 ng/mL of Nab-paclitaxel only, the cell viability significantly decreased compared to the control condition without Nab-paclitaxel (61 ± 2% vs 100 ± 0.1%; p < 0.001). BxPC-3 cells treated with Nab-paclitaxel at 2.5 ng/mL and exposed to ultrasound in the presence of BR38® MBs showed a slight but non-significant decrease in their viability in comparison to the treatment with Nab-paclitaxel alone. However, the combination of ultrasound with QA3216 MBs and 2.5 ng/mL of Nab-paclitaxel induced a significant decrease in the cell viability compared to the Nab-paclitaxel treatment alone (50 ± 2% vs 61 ± 2%; p < 0.01). All together, these results clearly show that QA3216 MBs in combination with ultrasound and Nab-paclitaxel induced a higher cell mortality compared to Nab-paclitaxel treatment alone.

**In-vivo Nab-paclitaxel delivery** - Subcutaneous pancreatic cancer tumors were treated with either QA3216 MB-assisted ultrasound on its own, or i.v. administration of Nab-paclitaxel at 5 or 20 mg/kg on its own, or by i.v. injection of Nab-paclitaxel at 5 or 20 mg/kg in combination with MB-assisted ultrasound and a co-administration of either QA3216 or BR38® MBs. The therapeutic effectiveness of Nab-paclitaxel delivery with or without MBs and ultrasound was monitored using anatomical ultrasound imaging every day before starting the treatment session. QA3216 MBs in combination with ultrasound application did not affect the tumor growth compared to the control group. In addition, the repeated i.v. administration of one Nab-paclitaxel dose at 5 mg/kg on its own led to a significant decrease in the tumor volume compared to control group ( p < 0.05). Furthermore, the combination of Nab-paclitaxel at 5 mg/kg with QA3216 MBs and ultrasound induced a significant and additional decrease in tumor volume after three treatments in comparison to Nab-paclitaxel treatment alone (Figure 2B; p < 0.05). The repeated i.v. injection of one Nab-paclitaxel dose at 20 mg/kg on its own resulted in a significant decrease in tumor volume compared to the repeated delivery of a Nab-paclitaxel dose at 5 mg/kg on its own or in combination with QA3216 MB-assisted ultrasound (p < 0.01). The repeated delivery of one Nab-paclitaxel dose at 20 mg/kg in combination with QA3216 MB-assisted ultrasound led to an additional and statistically significant decrease in tumor volume compared to the 20 mg/kg Nab-paclitaxel treatment alone (*p < 0.05). However, the combination of this chemotherapy with BR38® MB-assisted ultrasound resulted in a significant reduction in tumor volume until the 8th treatment in comparison to the 20 mg/kg Nab-paclitaxel treatment alone (#p < 0.05). No significant difference in the therapeutic effectiveness was
observed between both types of MBs for the repeated delivery of one Nab-paclitaxel dose at 20 mg/kg (Figure 2C). These results suggest that MB-assisted ultrasound potentiate the therapeutic effectiveness of one Nab-paclitaxel dose at 5 mg/kg as well as at 20 mg/kg in subcutaneous pancreatic cancer mouse model.

**Conclusions** – The present study showed that Nab-paclitaxel delivery using MB-assisted ultrasound enhanced the in-vitro and in-vivo therapeutic effectiveness of paclitaxel in comparison with Nab-paclitaxel treatment on its own.

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