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Cover story

Ultrasound and microbubble enhanced treatment of inoperable pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC) is currently the 4th most lethal cancer in the western world. It has an average 5-year survival of approximately 5%, and surgery provides the only possibility for a cure. However, more than 85% of newly diagnosed pancreatic tumors are considered unresectable due to locally advanced disease with encasement of large blood vessels or metastasis. Many (chemo)therapeutic options have been developed such as a nanoparticle albumin-bound paclitaxel (Nab-Paclitaxel), FOLFIRINOX, and even focused ultrasound surgery aimed to treat PDAC. Unfortunately, the reported increases in survival are incremental. It is necessary to continue our search for a therapy that will truly impact survival, provide a bridge to reductive surgery and ultimately cure PDAC. One approach that has shown great promise pre-clinically in a variety of solid tumors is sonoporation [1]. In sonoporation, microbubbles are injected intravascularly and the tumor is targeted using image-guided ultrasound [2]. Under specific ultrasound conditions the microbubbles interact with nearby cells, (i.e., within the tumor/vasculature) increasing the therapeutic efficacy resulting in tumor inhibition, most likely due to increased therapeutic agent in the targeted tumor and/or cell sensitization.

Publications by Professor Dimcevski and collaborators showed that sonoporation can inhibit tumor growth and metastatic spread in murine models [1]. In this issue, Professor Dimcevski and co-authors have performed the first clinical trial evaluating the toxicity and efficacy of sonoporation on human patients with PDAC [3]. The authors used commonly available clinical equipment, i.e., SonoVue® ultrasound contrast agent as the microbubbles of choice, and a GE Logiq 9 clinical diagnostic ultrasound scanner to induce sonoporation using low-intensity diagnostic ultrasound settings in the clinical regime. Gemcitabine was the chemotherapeutic of choice. Using the ultrasound generated image, the authors were able to directly target the tumor whilst minimizing treatment to the peripheral tissue. Sonoporation was initiated when the blood plasma concentration of gemcitabine was at its peak to increase local delivery without increasing systemic concentration of the drug.

After treating 10 patients, totaling 138 treatment cycles, no additional toxicity was observed. On average patients were able to undergo 14 treatment cycles. In contrast, the historical control cohort was only able to undergo an average of 8 treatment cycles. It is important to note that patients are only able to undergo chemotherapy treatment, if they are considered healthy and ambulatory. This indicated that the sonoporation treated patients were healthier for almost double the amount of time i.e., an increased period of high-quality of life. Overall survival was also improved in the sonoporation treated group. Specifically, sonoporation treated patients showed an average increase in survival of 8.7 months when compared to chemotherapy alone. In addition, 50% of the patients showed tumor recession, a phenomenon rarely observed in patients with PDAC.

The results from this clinical trial show great promise and open up a whole new era for targeted drug delivery. A benefit of this technique is that a plethora of solid tumors, using any therapeutic agent can be treated using such a protocol with little to no modification. One limitation to this technique is that the tumor must be able to be visualized using ultrasound so that microbubbles can enter it or the associated vasculature. This study provides encouraging data showing the clinical usefulness of sonoporation, and more clinical studies in the future are expected to generate more data for treating PDAC.

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