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Trial in Progress: Sonoporation for Disrupting the Pancreatic Cancer Microenvironment to Enhance Chemotherapy Delivery and Improve Outcomes

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Background

- Pancreatic ductal adenocarcinoma (PDAC) is 3% of cancers diagnosed in the United States with 62,210 new cases expected in 2022, but it is the fourth leading cause of cancer-related deaths.
- Hence, there is a considerable clinical need to develop innovative strategies for effective drug delivery and treatment monitoring, resulting in improved outcomes for patients with PDAC.
- Sonoporation is a novel method that can enhance the therapeutic efficacy of co-administered chemotherapy by localized contrast-enhanced ultrasound imaging (CEUS) of gas-filled microbubbles (ultrasound contrast agent UCA), which temporarily changes the tumor vascular microenvironment by increasing leakage from angiogenic vessels through microstreaming, shockwaves and the activation of various intracellular signaling responses [1].
- Our Phase I clinical trial of sonoporation in 10 PDAC patients treated with Gemcitabine demonstrated no additional toxicity and an increase in median survival compared to the standard of care treatment (8.9 vs 17.6 months; p = 0.011) [2].
- Subsequent, animal studies investigated 4 commercial UCAs under 2 different acoustic regimes and established the optimal UCA (Sonazoid; GE Healthcare, Oslo, Norway) as well as acoustic settings for sonoporation of PDAC [3].
- There are two major chemotherapeutic regimens for the treatment of non-resectable PDAC, a combination of Leucovorin, Fluorouracil, Irinotecan and Oxaliplatin (FOLFIRINOX), considered the first line treatment, or a combination of Gemcitabine with a nanoparticle formulation of Paclitaxel (Nab-Paclitaxel), the second line treatment. These regiments results in a median overall survival of approximately 11 and 8-9 months.
- The Oncological departments at Jefferson and Haukeland will be responsible for the SoC chemotherapeutic treatment. We will use the hospital's standard recommended treatment protocols of gemcitabine hydrochloride (Gemkabi®) combined with nanoparticle albumin-bound paclitaxel (Nab-Paclitaxel (Abraxane®)), and FOLFIRINOX.

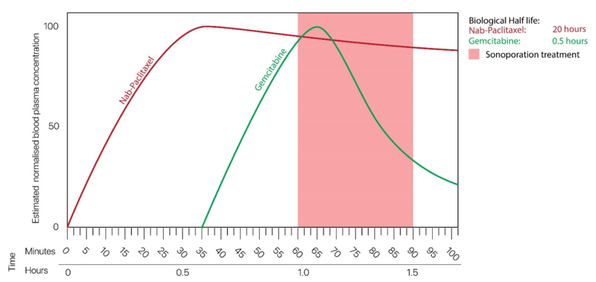

Figure 1: The estimated concentrations of Gemcitabine and Nab-Paclitaxel in blood plasma when the infusions are given in the previously described order. The red area is the window when the sonoporation treatment will be administrated.

Methods

- This Phase II clinical trial aims to improve standard of care (SoC) chemotherapy treatment by adding sonoporation (i.e., augmenting the SoC treatment with CEUS and microbubbles). Two sites (one in the USA and one in Norway) will enroll a total of 120 subjects with PDAC (stage 2 or higher) prior to starting SoC chemotherapy. Exclusion criteria include medically unstable patients, pregnant persons or anyone with known allergies to the UCA. The primary objective is to evaluate the safety and therapeutic efficacy of sonoporation on PDAC SoC treatment based on local progression-free and overall survival.
- Both male and female patients with histological verified metastatic or locally advanced (stages II, III or IV) PDAC, who meet the inclusion criteria, will be included. Patients will be randomly assigned to either the experimental (SoC chemotherapy + sonoporation) or control group (SoC alone) by the research coordinator using a random assignment generator.
- The oncologist in charge of the patient's chemotherapeutic treatment will decide whether the patient is to receive Gemcitabine/Nab-Paclitaxel or FOLFIRINOX as SoC, using the same parameters in decision making as would be done if the patient was not to be included in the study.
- In the experimental group the optimal CEUS and microbubble conditions will be applied to a single PDAC tumor imaged by ultrasound. Treatment will follow the timeline and guidelines of the SoC chemotherapeutic treatment for PDAC, with sonoporation performed immediately following each infusion of chemotherapy (when the concentration of drugs is maximum; Figs 1-2). Each sonoporation treatment will take 20 minutes of insonation with a constant sweep of the ultrasound probe so that the entire tumor receives the sonoporation treatment.

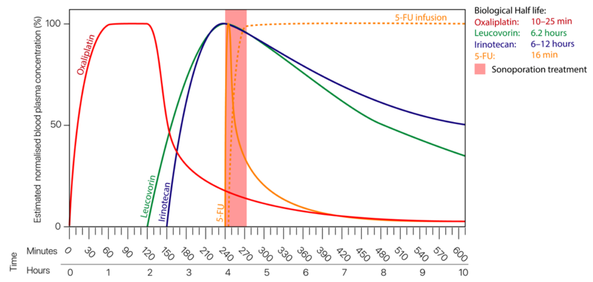

Figure 2: The estimated concentrations of Oxaliplatin, Leucovorin, Irinotecan and Fluorouracil in blood plasma when the infusions are given in the previously described order. The red area is the window when the sonoporation treatment will be administrated.

Methods (cont.)

- Gehan-Breslow-Wilcoxon test and Log-rank test will be used to compare survival. All clinical variables (e.g., concomitant imaging results, blood tests, etc.) will also be compared between groups with and without sonoporation.
- Following regulatory approvals (institutional IRBs, FDA under IND 153,874 and NCT04821284), 28 out of 120 subjects have been enrolled.

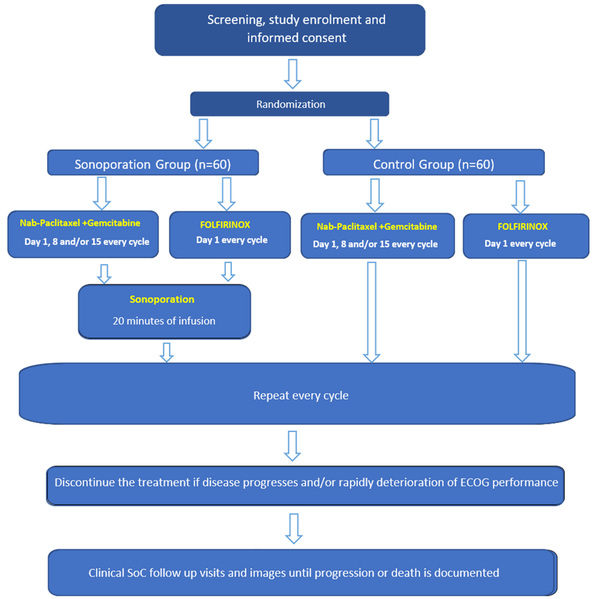

Figure 3: Study flowchart.

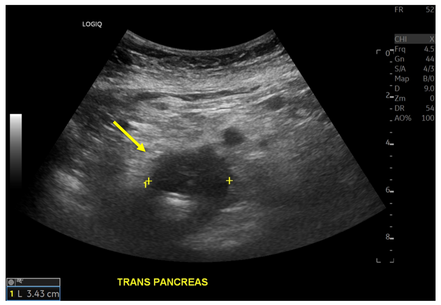

Figure 4: Ultrasound B-mode imaging from a case study. The image shows a tumor located at the head of the pancreas measuring 3.4 cm (arrow).

Methods (cont.)

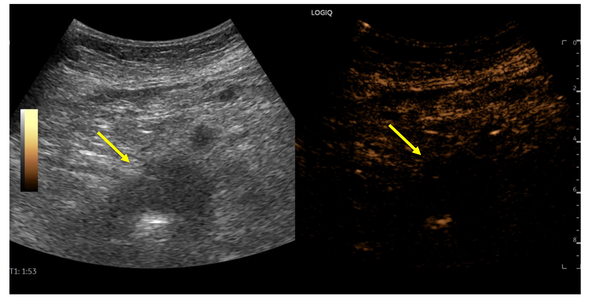

Figure 5: Ultrasound dual-image B-mode and CEUS from a case study. The arrows indicate the tumor in both a B-mode and CEUS. The CEUS image shows low vascularity inside the tumor characterized by the lack of marked enhancement.

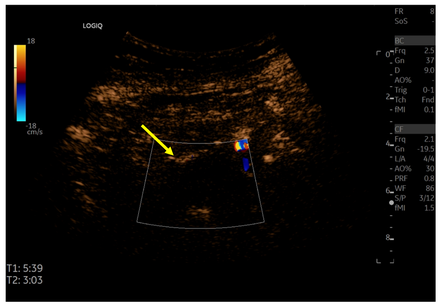

Figure 6: Sonoporation imaging example from a case study. The insonation of the tumor (arrow) is done by the use of the CEUS imaging mode with the addition of color Doppler imaging within the ROI positioned over the tumor. The Sonoporation treatment takes 20 minutes with constant sweeps to insonate the entire tumor.

References

1. Haugse et al. Pharmaceutics 12:1058, 2020.
2. Dimcevski et al. J Control Release 243:172-181, 2016.
3. Schultz et al. Cancer Biol Ther. 22:204-215, 2021.

Disclosure

- This work was supported by NIH grant R01 CA199646.
- The Logic E10 scanner was provided by GE Healthcare, Waukesha, WI, USA.
- The UCA Sonazoid was provided by GE healthcare, Oslo, Norway.

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