ISTU On-Air Webinar Series: August 27, 2020 Q & A

Joan Vidal-Jové M.D., Ph.D. presenting: "The Presence of FUS in Oncology: Linking Daily Oncology Practice with Basic Research"

#	Question	Answers
1	How did you manage treatment of a moving organ, such as liver?	Ultrasound guided devices allow treatment sonication view on real time, and make corrections if needed. Also, anesthesia with shallow breathing or jet ventilation are of good help, maintaining respiratory movements to a few mm.
2	Thank you for the presentation. It will be really helpful if you may share some thoughts about the following questions: Q1 What is the differences and advantages of using focused ultrasounds and sonoporation in cancer immunotherapy? Q2 How does the focused ultrasound alone (i.e. without microbubbles and chemo/immune drugs) influence the anti-inflammatory immune responses in the tumor microenvironment? Q3 How does the ultrasound attenuation influence the heat transfer of the local target zones? Will over-heat effects happen? How do these effects influences the suppressive tumor immunity?	Q1: Both have proven their effects in experiments activating the response due to immunotherapy. Probably Focused Ultrasound with Histotripsy obtains a bigger effect. Q2: In previous reports by the group of the Michigan University this is due to increases in CD8+ T cells, tumor specific CD8+ T cells, as well as natural killer (NK) cells, dendritic cells (DC), neutrophils and macrophages. Q3: We have seen over heat effects with Focused Ultrasound thermal when treating near bone structures that have mirror effect on skin or subcutaneous fat. This may suppress immunity effects mediated by citoquines but activate Heat Shock Proteins. With Histotripsy we have not seen overheat effects.
3	What would be “best” immunotherapies to combine with FUS for PDA?	In the ones available today I have low experience, but I would explore Pembrolizumab or Atezolizumab.
4	Is there any bleeding issue/problem after applying histotripsy?	We have not seen this complication in the cases treated until today, In the monitoring image tests with MRI or CEUS vessels inside the ablation zone were respected and seen clearly.
5	To what extent have the pro-inflammatory effects of histrotypsy and thermal ablation been shown in vivo? How durable are they, and is there an anti-inflammatory response intiated in the PDAC stroma to compensate?	In the mouse model, the group of the Michigan University has seen increased inflammatory response. Flow cytometric analysis demonstrated significant increases in CD8+ T cells, tumor specific CD8+ T cells, as well as natural killer (NK) cells, dendritic cells (DC), neutrophils and macrophages at Day 10 following histotripsy compared to untreated controls and ultrasound thermal therapy in both the local ablated tumor and the abscopal tumor. In our human patients we have not seen the same effect clearly, but probably there is not enough data.
6	I noticed you treated the left lobe of the liver which is more exposed. Do the ribs cause problems for Histotripsy?	We have not seen problems because that was not the aim of the study. The new generation device seems that it has this problem solved.
7	How do you manage bowel gas?	With US guided device we see the gas and we can avoided, either with a water balloon compressing the abdomen and rejecting the bowel to the sides. But this can only apply to gas in noir fixed structures for instance small bowel. With duodenum or colon it is more difficult.
8	How long is the treatment time for 3x3x3 tumor?	We count about 10-15 minutes for each cm. That would be between 30-45 minutes. That including only treatment time, not preparing or positioning the patient.
9	What is the advantage of treating tumors with histotripsy compared to HIFU? And how long does treating a tumor about 1cm3 take with histotripsy?	Histotripsy is faster, more clear cut treatment, no thermal effects on the surrounding tissues or structures, respects vessels and ducts with different tissue properties, and generates a better immune response.
10	Are you worried about downstrem metastases when using histotripsy?	As I would be with any ablation. At this point, all research results had not proven any problem related with that. But we need to follow more time these patients.
11	Q1: Is histotripsy safe ? and can it clinically be used? Q2: Can it already be used in combination with checkpoint inhibition?	Q1: In our study, we did not find any major adverse event, no pain, no bleeding complications, no clotting problems. We are about of initiate the following trials in that direction. Q2: I would love to do this trial. I believe it should be consider when the device is commercially available.
12	About the Caltech (last) paper: which are the acoustic differences between cancer cells and healthy cells?	It seems that differences are related to harmonics or resonance natural frequencies of the cells. Low intensity pulsed ultrasound only affects malignant cells.
13	With ultrasound guidance, how do you monitor the FUS dose.	It is very difficult, I do not think there is a commercially available device that can do it. What we do is see the ultrasound changes seen on ablated tissues to consider that the treatment is completed .
14	Based on your experience, which one of the therapy modalities, namely HIFU, LIPUS, histotripsy and LIFU, is more effective in inducing the abscopal effect?	I think that now Histotripsy seems to be number one.
15	Can you monitor heat using acoustics?	No, I do not think that is available today, may be indirectly, but I do not know.
16	How many sonications do you need to cover the tumor completely? Have you thought of acoustic holography to need only a single sonication for the whole tumor geometry?	Sonications generate around 1 mm ablation, depending on intensity applied. I have not thought on acoustic holography, it would be interesting to research, but we would have to consider precision of the target.
17	Would you recommend HIFU of LiFU for T1-T2 tumors?	Yes, but depending on the organs: breast and liver would be the first ones to research.
18	How do you monitor the FUS dose?	That is answered in questions 13 and 15.
19	Are there limits of Histotripsy regarding size, such as in cryoablation due to cryo shock?	The group of the Michigan University in mouse experiments, has seen some severe side effects when treating a very large tumor volume in one single treatment by histotripsy, which suggests that there may be an upper size limit for one treatment. This size limit may be different depending on the organ. We are considering multiple treatment sessions for larger tumors, which might also be beneficial for stimulating the immune response.