

Proof of Concept Clinical Trial of Hyperpolarized C-13 Pyruvate in Patients with Prostate Cancer

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Introduction: In vivo hyperpolarized C-13 metabolic imaging is an exciting new technology for observing changes associated with malignant transformation and response to therapy [1]. Pre-clinical studies in prostate, brain, kidney, liver and breast cancers, as well as in lymphoma have indicated that acquiring data after the injection of hyperpolarized C-13 pyruvate can be used to monitor spatial and temporal changes in the ratio of lactate to pyruvate [2]. Higher baseline levels of lactate/pyruvate were shown to indicate the presence of more aggressive/higher grade tumor [3] and a reduction in lactate/pyruvate within 1 to 4 days after treatment was provided an early indication of response that occurred prior to changes in tumor size on anatomic images [4]. The goal of our study was to demonstrate the safety and feasibility of applying this technology for the first time to patients with prostate cancer.

Methods: Patients with biopsy-proven prostate cancer being followed with active surveillance were screened to ensure that they met clinical criteria for participating in the study. The 3+3 design that is commonly used in phase I trials of new treatments for dose escalation was modified in order to consider 6 patients at each dose levels; 3 patients for whom the data acquisition was designed to monitor the kinetics of the dose delivery and 3 patients for whom the data acquisition focused on the spatial distribution of metabolism in tumor versus normal prostate. Once the dose escalation component was completed, the study design called for data to be obtained from 15 additional patients to obtain additional information about the biological variability of metabolism. Entry into the study required that the patient be untreated, pass clinical screening, and had received a recent high spatial resolution MRI/H-1 MRSI staging exam using a H-1 phased array abdominal coil and endorectal coil. This meant that they were familiar with MR procedures. The hyperpolarized C-13 pyruvate was produced using a modified version of the initial proof of concept DNP system [5] that resides in a clean room adjacent to our 3T whole body MR scanner. The formulation was designed to provide 250mM pyruvate. Procedures for generating, performing an automated QC assessment and delivering the sterile agent were developed by imaging scientists and pharmacists at UCSF, in collaboration with engineers from GE Healthcare. Other critical hardware components were a custom designed volume C-13 transmit coil and a H-1/C-13 endorectal receive coil that were used in conjunction with a 3T whole body scanner. Methods for acquiring and analyzing the C-13 MR data were initially developed in pre-clinical studies using rodent and dog models, with further refinement as the study progressed. Prior to the exam and IV was set up and patients were monitored with tests that included EKG, vital sign, liver function, hematology and urine assessments. Anatomic images were acquired first, followed by the dissolution, confirmation that the agent passed quality control criteria and rapid injection into the patient with timed C-13 data acquisition. Clinical monitoring continued for 4 hours after the exam and was repeated 24 hours and one week later. The study received IND approval from the FDA and IRB approval from UCSF.

Results: A total of 33 patients received the MR examination, with 31 successfully receiving an injection of the hyperpolarized agent. The majority had a diagnosis of Gleason grade 6 tumors, with 6 having grade 7 and 2 grade 8. Their median age was 63 (range 45-75) and median PSA was 5.9 (range 1.88-20.2). Two samples had low polarization due to hardware failure and were not injected. For the 31 samples that were injected the average polarization was 17.8% (15.9-21.1), average pH 7.6 (7.3-8.0), average temperature 32.4 degrees (28.8 to 36.4) and average volume 51.9cc (31.9-53.5). These were all within the pre-defined QC criteria and were approved for injection by the pharmacist who was present to monitor the procedure. The dissolution process took an average of 17.8s (5-30), the QC process 13.1s (10-19), the delivery through the hatch into the scan room 21.8s (11-30) and the injection 14.9s (6-28). Overall this gave an average of 67.6s (43-88) for delivery from time of dissolution to the subject. There were no dose limiting toxicity observed at the 3 levels considered (0.14, 0.28 and 0.43 mL/Kg body weight). The highest dose was established as the MTD. Nine patients were studied with dynamic MRS with 1-D EPSI spatial localization, 5 with dynamic MRS and 2-D spatial localization (1-D EPSI, 1-D phase encoding), 6 with 2-D single time point MRSI (2-D phase encoding) and 11 with single time point 3-D MRSI (1-D EPSI, 2-D phase encoding).

Figures 1 and 2 show examples of data obtained from two different subjects and clearly demonstrate that pyruvate not only got to the prostate but that its metabolic

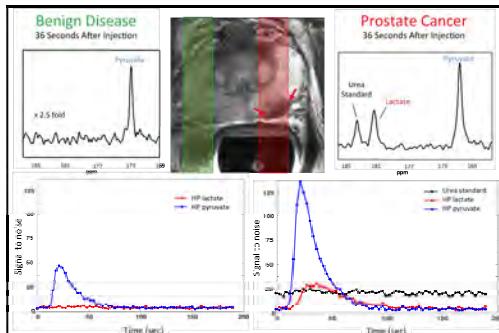


Figure 1. Dynamic C-13 data from a patient injected with 12cc of hyperpolarized pyruvate (lowest dose).

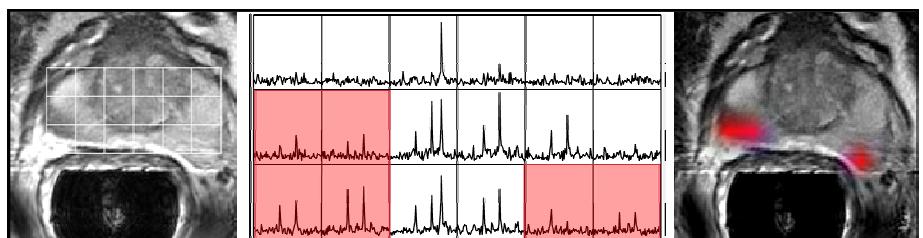


Figure 2: C-13 MRSI data from a patient with a biopsy-proven bilateral cancer of Gleason grade 3+3 in 8/12 cores and PSA of 4.58. There is an abnormality seen on the T2 weighted images on the right but not on the left. The array of C-13 spectra shows voxels that have peaks at the left-most frequency of lactate and at the right-most frequency of pyruvate. The voxels shaded red have clearly elevated lactate/pyruvate compared to the normal appearing prostate. The overlay of lactate/pyruvate in red on the far image further highlights the presence of abnormal signal on both sides of the prostate.

product lactate is observed. The dynamic data in Figure 1 data are from a slice through the tumor region and show the maximum of pyruvate (in blue) occurs around 5-10 seconds prior to the maximum of lactate (in red). On the contralateral side there is virtually no lactate observed and the pyruvate is much lower. The black line is from the urea standard, which is partially included in the slice that goes through the tumor. The MRSI data in Figure 2 that was obtained from a patient who was injected with the highest dose and suggest that the lactate/pyruvate may be able to help in localizing tumor, even in the absence of a clear lesion on the T2 lesion.

Conclusions: We have successfully applied hyperpolarized C-13 metabolic imaging with pyruvate in a clinical trial of patients with prostate cancer. There were no dose limiting toxicities observed and the MTD was established at 0.43mL/Kg of 250mM pyruvate. Signals from pyruvate and lactate were observed in the vasculature, tumor and normal prostate at all three doses but, as expected the highest dose showed the best SNR for pyruvate and clearest distinction in lactate/pyruvate between tumor and normal prostate. Future studies using improved methods for higher polarizations and faster delivery will move in three complementary directions. The first is to use the same technology to evaluate changes in lactate/pyruvate that occur in patients exposed to a therapeutic intervention, the second is to apply similar methods to patients with other types of cancer and the third is to take advantage of the new Spinlab polarizer that is being designed to provide higher polarizations, to shorten the time to injection, to provide up to four samples at the same time and to use a sterile fluid path that no longer requires polarization in a clean room.

References: [1] Golman et al. Can.Res 2006, [2] Chen et al. MRM 2007, [3] Albers et al. Can.Res. 2008, [4] Park et al. JMRI. 201, [5] Ardenkjaer-Larsen et al. PNAS 2003

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