Effect of cabozantinib on K^{trans} and v_e values in castration-resistant prostate cancer

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TARGET AUDIENCE: Oncologists; Radiologists; Medical physicists developing quantitative DCEMRI techniques.

PURPOSE: Cabozantinib shows promising results in early clinical trials for men with castration-resistant prostate cancer, particularly with regards to bone metastases, in which resolution of bone scans, and significant improvement in bone pain has been reported with the medication.[1,2] In this preliminary report, we document the effect of cabozantinib on perfusion in bone metastases in castration-resistant prostate cancer and in muscle tissue using the Tofts model parameters K^{trans} and v_e.

METHODS: In an IRB-approved and HIPAA-compliant clinical trial of cabozantinib, male patients with castrate resistant prostate cancer were accrued after informed consent was given. Nine patients were scanned with dynamic contrast-enhanced MRI (DCEMRI) at least once prior to cabozantinib therapy (Screen, W0) and at week 2 (W2) following the initiation of therapy. Further MRI scans at every 12 weeks following the initiation of therapy (W12, W24) were performed but are not analyzed here. The DCEMRI scans were done using a T1-weighted sequence, with 2x2x5 mm^3 voxels, TR/TE 7.5/2.85 ms, flip angle 10°, and 10 s temporal resolution. A standard dose of 0.1 mmol/kg of gadodiamide (Omniscan, GE, Waukeesha, WI) was injected in under 10 s. The reference tissue method, published earlier, was used to determine the concentration of the contrast agent in muscle and bone metastases.[3] K^{trans} and v_e were determined from the concentration time curves defined over regions of interest, using the Tofts model[4] and the population AIF.[5] The primary endpoint of the study was K^{trans} change at week 2 (W2), and the values of K^{trans} and v_e in the pre- and post-treatment scans were compared using the one-tailed non-parametric Wilcoxon signed-rank test.

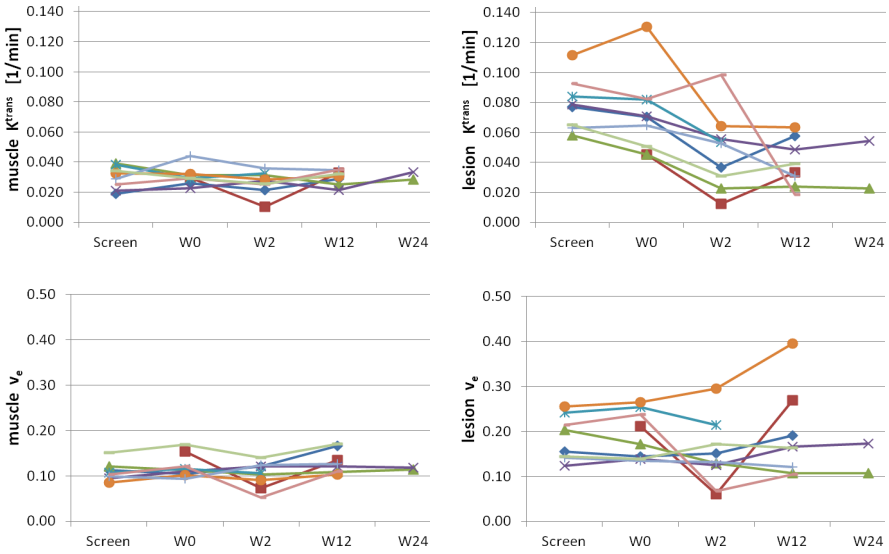

Figure 1: K^{trans} (top) and v_e (bottom) values are shown for muscle (left) and lesions (right), at each time point (Screen, W0-W24), for 9 patients.

	Pre-treatment average (Screen, W0)	First post-treatment average (W2)	Change [%]	p-value
K^{trans} [min^{-1}]				
Muscle	0.030 ± 0.005	0.027 ± 0.007	-11 ± 24	0.07
Lesion	0.073 ± 0.023	0.047 ± 0.026	-37 ± 25	**< 0.01**
v_e				
Muscle	0.12 ± 0.02	0.10 ± 0.03	-9 ± 29	0.25
Lesion	0.19 ± 0.05	0.15 ± 0.07	-18 ± 34	0.10

Table 1: Values of two-compartment model parameters, averaged over all subjects

RESULTS: The time-dependent plots of K^{trans} and v_e measured in muscle and metastatic bone lesions are shown in Figure 1 for all patients. The muscle values show less variability than the values measured in lesions. Overall average values, their change following initiation of therapy, and the corresponding p values are listed in Table 1. There was a statistically significant decrease in lesion K^{trans} (37% on average, $p < 0.01$, bold) during the first two weeks of therapy, while other quantities were not significantly changed.

DISCUSSION AND CONCLUSION: In this preliminary report, the population AIF was used to determine K^{trans} and v_e in the muscles, and therefore the variations in the AIF due to e.g., varying cardiac output, were not accounted for, which may cause small inaccuracies in the absolute measurement of K^{trans} and v_e values. However, an average overall decrease in lesion K^{trans} was measured. It remains to be seen whether this decrease will remain with further accrual, and whether individual changes in lesion K^{trans} will be correlated with treatment response.

1. Lee, et al., *Clin Cancer Res* 2013, **19**(11): 3088.
2. Smith, et al., *J Clin Oncol* 2013, **31**(4): 412.
3. Medved, et al., *J Magn Reson Imaging* 2004, **20**(1): 122.
4. Tofts, et al., *J Magn Reson Imaging* 1999, **10**(3): 223.
5. Parker, et al., *Magn Reson Med* 2006, **56**(5): 993.