Estimation of cellular glutamine pool size in breast cancer by [^{18}F](2S,4R)4-Fluoroglutamine PET: a quantitative kinetic approach

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INTRODUCTION

Reprogramming energy metabolism is an emerging hallmark of cancer.[1] Imaging the glucose analog FDG has gained widespread clinical acceptance. Imaging glutamine metabolism has been largely studied in preclinical models, with an early human study showing uptake of [^{18}F](2S,4R)4-Fluoroglutamine ([^{18}F]FGln) in gliomas.

Zhou et al. recently studied [^{18}F]FGln in breast cancer xenografts with different levels of glutaminase activity, the first enzyme in glutaminolysis.[2] Magnetic resonance spectroscopy (MRS) demonstrated low cellular glutamine pool size in triple-negative breast cancer (TNBC) tumors with high glutaminase activity and high glutamine pool size in MCF-7 tumors with low glutaminase activity. Upon glutaminase inhibition, glutamine pool size increased in TNBC, but not MCF-7, tumors. Tumor to blood ratios (T/B) of [^{18}F]FGln obtained from static images paralleled the MRS findings.

[^{18}F]FGln shares the same cellular transporters as glutamine, but is minimally metabolized, making it an ideal radiotracer to track intracellular glutamine pool size through estimates of distribution volume (V_D). In this study, we analyze the kinetics of [^{18}F]FGln in two mouse models.

METHODS

TNBC (HCC1806) and receptor-positive (MCF-7) xenografts were established. PET scans were performed on a dedicated small animal scanner at baseline and after treatment with the glutaminase inhibitor CB-839 (Calithera) or a vehicle solution. Dynamic PET images, the majority obtained in list mode for early time points, were obtained for one hour after i.v. injection of 300-350 μCi [^{18}F]FGln. Images were analyzed with AMIDE. Kinetic analysis was performed on a representative mouse with PMOD.

RESULTS

An image-derived input function was obtained. Logan plot analysis demonstrated late linearity and k_3 in a two-compartment model with irreversible trapping was small (most < 0.01/min), consistent with minimal trapping. At baseline, MCF-7 tumors demonstrated increased T/B and V_D compared to TNBC tumors, as estimated by a Logan plot and a single-compartment model (>60% larger). Upon glutaminase inhibition, T/B and V_D increased in the TNBC (mean >30%), but not in the MCF-7 tumors. These findings are consistent with MRS estimates of glutamine pool size. A strong correlation was seen between T/B and V_D by Logan plot and a single-compartment model, but not with a two-compartment model.

Sensitivity analysis of a two-compartment model revealed relative insensitivity of k_3 compared to K_1 and k_2. Monte Carlo simulations with noise added to the model curve demonstrated greater standard error of $k_3$compared to K_1 and k_2. These findings, together with biologic data, suggest studying a single-compartment model. When compared to a single-compartment mode, the two-compartment model has a slightly lower AIC (38 versus 40.8).

CONCLUSION

Through multiple techniques, [^{18}F]FGln has been shown to track glutamine pool size. Kinetic analysis of this radiotracer provides insight into accurate image interpretation. [^{18}F]FGln imaging holds promise in assessing pharmacodynamic effect of targeted therapy, specifically CB-839 which has advanced into early clinical trials.

REFERENCES

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2: 28202527