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Potential for Increasing Tumor Uptake of Radiolabeled MIBG and/or DOTATOC in Patients with Mid-Gut Neuroendocrine Tumors Using a Histone Deacetylase Inhibitor

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BACKGROUND: Histone deacetylase inhibitors (HDACI) upregulate norepinephrine transporters and increase uptake of 123I-MIBG in neuroblastoma and pheochromocytoma in preclinical studies. HDACIs upregulate many cellular proteins, and given the similarities between neuroblastoma and the more common mid-gut neuroendocrine tumors (MGNET), further exploration of HDACI effects on the latter is warranted. This pilot study focuses on metastatic MGNETs in humans and evaluates the effect of pretreatment with the HDACI vorinostat on norepinephrine transporter and somatostatin receptor expression by way of 123I-MIBG and 68Ga-DOTATOC imaging.

METHODS: Clinically stable MGNET subjects with liver metastases were imaged at baseline and again ~4 weeks later after vorinostat (300mg PO daily for 4 days with tracer injection on day 4). 300mg rather than 400mg (maximal FDA dose) was chosen to reduce side effects. Imaging was performed ~4 weeks post-LAR administration with strict attention to timing/technique. PET/CT was performed using 5 mCi 68Ga-DOTATOC; %SUVmax change per tumor was calculated [(SUVvorinostat-SUVbaseline)/SUVbaseline]. SPECT/CT was performed 24 hours following 10 mCi I-123 MIBG; ratio images of the liver (created by dividing the

vorinostat scan by the baseline scan) were assessed qualitatively to determine effects on tumor uptake.

RESULTS: Liver metastases in 5 subjects (n=50, 10 tumors per subject, mean size 2.1±1.0 cm) were evaluated. There was no significant difference in administered activity or uptake time between pairs of scans. Mild increase in tumor SUVmax post-vorinostat was noted (total group mean: +11%, $p<0.01$; range of group mean per subject -15% to +26%). Normal liver SUVmax showed no change ($p=0.12$). There was no appreciable change in MIBG tumor uptake post-vorinostat based on ratio images.

CONCLUSION: Our findings suggest that a short course of vorinostat may be enhance MGNET uptake of 68Ga-DOTATOC and therefore potentially 177Lu-DOTATOC. No appreciable effect was detected for MIBG. It may be useful to study the effect of longer vorinostat treatment at higher doses.