Potential for increasing tumor uptake of radiolabeled ^{123}I-MIBG and/or ^{68}Ga-DOTOTOC using a histone deacetylase inhibitor in patients with mid-gut neuroendocrine tumors

Janet Pollard, MD[1]; David Bushnell, MD[1]; Yusuf Menda, MD[1]; Mark Madsen, MD[1]; Tom O'Dorisio, MD[1]; Sue O'Dorisio, MD[1]; Gideon Zamba, MD[1]; Tim Ginader, MD[1]; Laura Ponto, PhD[1]

[1]University of Iowa Hospitals and Clinics. Contact: janet-pollard@uiowa.edu Disclosures: None

Purpose

- This study focuses on mid-gut neuroendocrine tumors metastatic to the liver and evaluates the effect of pretreatment with the histone deacetylase inhibitor vorinostat on expression of norepinephrine transporter and somatostatin receptors in humans by way of imaging with ^{123}I-MIBG and ^{68}Ga-DOTATOC.

Background

- Vorinostat is a chemotherapeutic agent in the histone deacetylase (HDAC) inhibitor family.
- Histone deacetylase inhibitors such as vorinostat upregulate norepinephrine transporters and increase uptake of ^{123}I-MIBG in neuroblastoma and pheochromocytoma in preclinical studies.
- Preclinical studies have shown that vorinostat upregulates cellular norepinephrine transporters and uptake of ^{123}I-MIBG in neuroblastoma cell lines and *in vivo* in neuroblasoma mouse models (Clin Cancer Res 2011; 17: 2339-2349), and other HDAC inhibitors increase uptake of this radiotracer in pheochromocytoma cell lines (Endocr Relat Cancer 2011; 18: 143-157). The effects of vorinostat on somatostatin receptor expression is not known.
- HDAC inhibitors upregulate many cellular proteins beyond this, and given the similarities between neuroblastoma and the more common mid-gut neuroendocrine tumors (NETs), further exploration of the effects of these drugs on NETs is warranted.

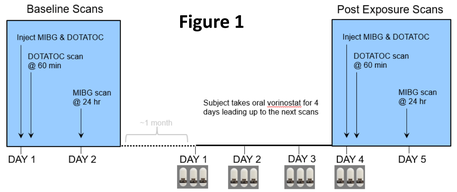
Methods – Subject Eligibility

- Eligible subjects were those with clinically stable midgut NET with liver metastases measuring at least 2 cm in diameter on MRI or CT and who had not undergone PRRNT therapy within the last year.
- Subjects on long-acting octreotide injections were required to be at the same dose level for at least 3 months prior to the study.

Methods – Dosing and Imaging

- This was a prospective pilot study using test and re-test design.
- Subjects were imaged at baseline and again about 4 weeks later after a short course of vorinostat (Fig. 1). Strict attention was given to timing/technique of the scans.
- Subjects were imaged just before their monthly injection of long-acting octreotide. Subjects were asked to abstain from over-the-counter sympathomimetic drugs.
- Vorinostat dosing: 300mg PO each day for four days. 300mg rather than 400mg (maximal FDA dose) was chosen to reduce side effects.
- Subjects were pre-treated with oral saturated solution of potassium iodide.
- SPECT/CT was performed with 10 mCi ^{123}I-MIBG and a 24 hour uptake period.
- PET/CT was performed with 5 mCi ^{68}Ga-DOTATOC and 60 min uptake period.

Figure 1



Methods – Imaging Analysis

- PET/CT
  - Lesion analysis with a region of interest was performed in 10 of the largest discrete tumors per subject (Fig. 2).
  - Percent change in SUVmax per tumor was calculated [(SUVvorinostat – SUVbaseline)/SUVbaseline] for PET/CTs
- SPECT/CT
  - Ratio images of the liver (created by dividing the vorinostat scan by the baseline scan) were assessed qualitatively to determine effects on tumor uptake (fig. 3 and 4).

Methods – Imaging Analysis (Cont'd)

Figure 2

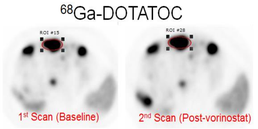


Figure 3

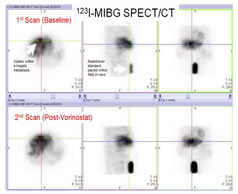
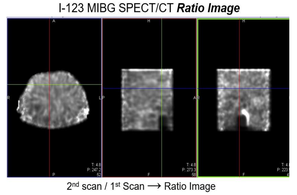


Figure 4



Results

- PET/CT ^{68}Ga-DOTATOC findings:
  - Liver metastases in 5 subjects were evaluated (n=50, 10 tumors per subject, mean size 2.1±1.0 cm).
  - Mild increase (+11%, p<0.01) in total group mean tumor SUVmax post-vorinostat; range of group mean per subject -15% to +26%) (Tables 1-6)
  - No significant difference in administered activity or uptake time between pairs of scans
  - No significant change in normal background liver SUVmax (p=0.12).
  - Mild increase trending towards significance of normal liver SUVmean (p=0.07)
- SPECT/CT ^{123}I-MIBG findings:
  - No appreciable change in tumor uptake based on qualitative ratio images
- No adverse events greater than grade 1 were encountered. These events were possibly attributable to vorinostat.

Table 1-5

Mean SUVmax of Ten Tumors in Each Subject Before and After Vorinostat

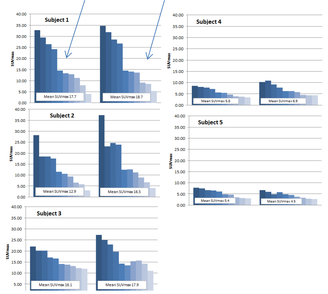
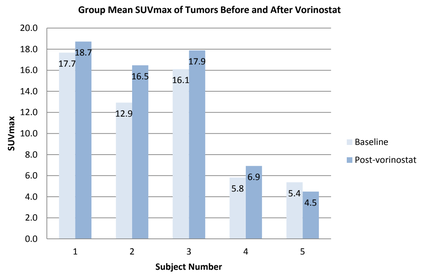


Table 6



Conclusion

- Our findings suggest that a short course of vorinostat may enhance uptake in metastatic mid-gut NET of ^{68}Ga-DOTATOC and therefore potentially ^{177}Lu-DOTATOC. No appreciable effect was detected for ^{123}I-MIBG.
- It may be useful to study the effect of longer vorinostat treatment at higher doses.

References

- More SS, Itsara M, Yang X, Geier EG, Tadano MK, Seo Y, et al. Vorinostat increases expression of functional norepinephrine transporter in neuroblastoma *in vitro* and *in vivo* model systems. *Clin Cancer Res* 2011; 17: 2339-2349.
- Bose P, Dai Y, Grant S. Histone deacetylase inhibitor (HDACI) mechanisms of action: Emerging Insights. *Pharmacol Ther.* Published Online First April 24, 2014 http://www.sciencedirect.com/science/article/pii/S0163725814000928
- Zolinza (vorinostat) Full Prescribing Information (package insert). Merck & Co. 4/20/2013.
- Bushnell DL, Baum RP. Standard Imaging Techniques for Neuroendocrine Tumors. *Endocrinol Metab Clin* N Am 40 (2011) 153-162.
- Skoura E, Papachristou M, Datseris IE. The Role of Nuclear Medicine in Imaging and Therapy of Neuroendocrine Tumors. *Hospital Chronicles* 2012, 7(2): 81-90.
- Menda Y, Boles Ponto LL, Schultz MK, Zmaba GKD, Watkins GL, et al. Repeatabiltiy of Gallium-68 DOTATOC Positron Emission Tomographic Imaging in Neuroendocrine Tumors. *Pancreas* 2013; 42: 937-943.
- Quaedvlieg PFHJ, Visser O, Lamers CBHW, Janssen-Heijen MLG, and Taal BG. Epidemiology and survival in patients with carcinoid disease in the Netherlands. An epidemiological study with 2391 patients. *Ann Oncol* 2001; 12: 1295-1300.
- Ezziddin S, Logvinski T, Yong-Hing C, Ahmadzadehfar H, et al. Factors Predicting Tracer Uptake in Somatostatin Receptor and MIBG Scintigraphy of Metastatic Gastroenteropancreatic Neuroendocrine Tumors. *J Nucl Med.* 2006; 47: 223-233.
- Martinoiva L, Perera SM, Brouwers FM, Alesci S et al. Increased uptake of 123I meta-iodobenzylguanidine, 18F fluorodopamine, and 3H norepinephrine in mouse pheochromocytoma cells and tumors after treatment with the histone deacetylase inhibitors. *Endocr Relat Cancer.* 2011; 18: 143-157.
- Zuetenhorst JM, Taal BG. Metastatic Carcinoid Tumors: A Clinical Review. *Oncologist.* 2005, 10: 123-131.
- Kronenberg HM et al. *Williams Textbook of Endocrinology.* Chapter: Carcinoid Tumors, Carcinoid Syndrome, and Related Disorders. Saunders 12 e: 2011.
- Taal BG, Visser O. Epidemiology of Neuroendocrine Tumours. *Neuroendocrinology*. 2004; 80 (suppl 1): 3-7.
- Yao JC, Hassan M, Phan A, Dagahoy C et al. One Hundred Years After "Carcinoid": Epidemiology of and Prognostic Factors for Neuroendocrine Tumors in 35,825 Cases in the United States. 2008. J Clin Oncol 25: 3063-3072
- Rubin EH, Agrawal GB, Friedman EJ, Scott P et al. A Study to Determine the Effects of Food and Multiple Dosing on the Pharmakokinetics of Vorinostat Given Orally to Patients with Advanced Cancer. Clin Cancer Res 2006; 12 (23) 7039-7045.
- Liu Z, Marquez M, Nilsson S, Holmberg AR. Incubation with somatostatin, 5-aza decitabine and trichostatin up-regulates somatostatin receptor expression in prostate cancer cells. 2008. Oncol Rep 20: 151-154, 2008.

Funding

NIH/NCI Grant Number: 1P50CA174521 Grant Title: Neuroendocrine Tumor Specialized Programs of Research Excellence (SPORE) in Human Cancer – Career Development Award