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

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Purpose
- This study focused on mid-gut neuroendocrine tumors metastatic to the liver and evaluated the effect of pretreatment with the histone deacetylase inhibitor vorinostat on expression of somatostatin receptor and somatostatin receptors in humans by way of imaging with \(^{123}\text{I-MIBG}\) and \(^{68}\text{Ga-DOTOTOC}\).

Background
- Vorinostat is a chemotherapeutic agent in the histone deacetylase (HDAC) inhibitor family.
- Histone deacetylase inhibitors such as vorinostat upregulate nipecotic acid transporters and increase uptake of \(^{123}\text{I-MIBG}\) in neuroblastoma and pheochromocytoma in preclinical studies.
- Preclinical studies have shown that vorinostat upregulates cellular nipecotide transporters and uptake of \(^{123}\text{I-MIBG}\) in neuroblastoma cell lines and in vivo in neuroblastoma 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 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 mid-gut NET with liver metastases measuring at least 2 cm in diameter on MRI or CT and who had not undergone PRRT therapy within the last year.
- Subjects on long-acting nipecotide 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 technigiques of the scans.
- Subjects were imaged just before their monthly injection of long-acting nipecotide. Subjects were asked to abstain from over-the-counter symptomatic drugs.
- Vorinostat dosing: 300mg PO each day for four days.

Results
- **PET/CT \(^{123}\text{I-MIBG}\) findings:**
  - Liver metastases in 5 subjects were evaluated (n=5, 10 tumors per subject, mean size 2.1±1.0 cm).
  - Mild increase (+11%; p=0.02) in total group mean liver 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 SUVmax (p=0.12).
  - Mild increase trending towards significance of normal liver SUVmean (p=0.07).

- **PET/CT \(^{123}\text{I-MIBG}\) findings:**
  - No appreciable change in tumor uptake based on qualitative ratio images.
  - No adverse events greater than grade 3 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: Group Mean SUVmax of Ten Tumors Before and After Vorinostat

**References**
- Zonda cordisium IV (Prescribing Information). Merck & Co. 4/20/2013.

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

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