Magnetic Resonance Spectroscopic Imaging Measurement of Early Response to Vorinostat Treatment in Recurrent Glioblastoma

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Background

A major impediment to the development of new therapies for glioblastoma is a lack of biomarkers indicating response. The current standard for assessing tumor progression relies on changes in size of the enhancing components of the tumor on standard MRI. Epigenetic modifications are now recognized as a frequent development in the early phases of tumorigenesis, playing a central role in tumor development. Epigenetic alterations differ significantly from genetic modifications in that they may be readily revertible by "epigenetic drugs'' such as inhibitors of histone deacetylases (HDAC). HDACs As a promising new modality for cancer therapy the first generation of HDAC inhibitors (HDACi) are currently being tested in phase I/II clinical trials. Glioblastomas benefit from therapy with HDACi, such as vorinostat, or SAHA, demonstrating tumor redifferentiation/cytostasis rather than tumor size reduction. This limits the utility of traditional imaging methods such as MRI. Magnetic resonance spectroscopic imaging (MRSI) quantitates amino acids and other metabolic substances in tumor and normal brain, allowing characterization of metabolic processes in live tissue.

Preclinical Findings

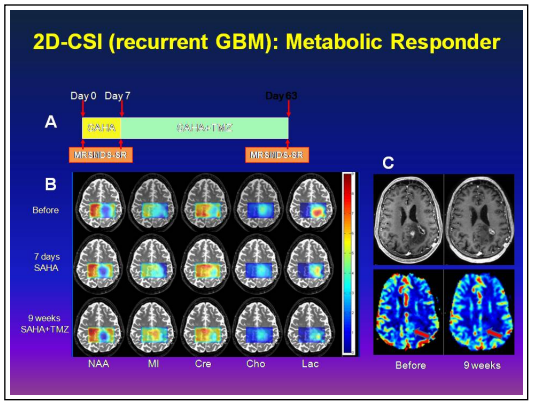
Preclinical study (L. Wei et al. NMR in Biomedicine 2012) showed

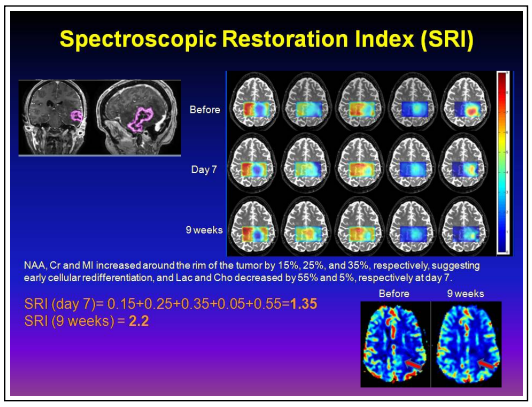
(1)Normalization/restoration in 1H MRS metabolites could be reliable biomarkers for an early response to vorinostat in an orthotopic animal model for glioma.

(2)Reduced inositol and NAA were found to be potential biomarkers for mood alteration and depression, which may also be alleviated with vorinostat treatment.

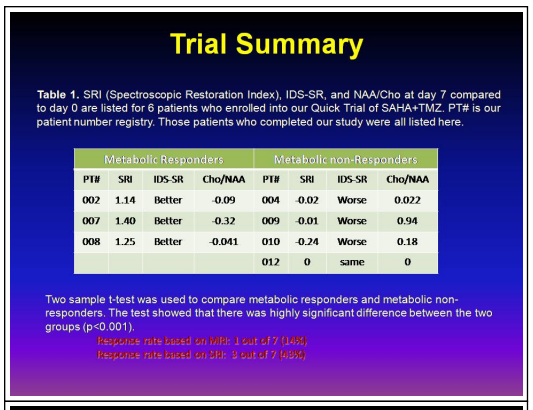
Results

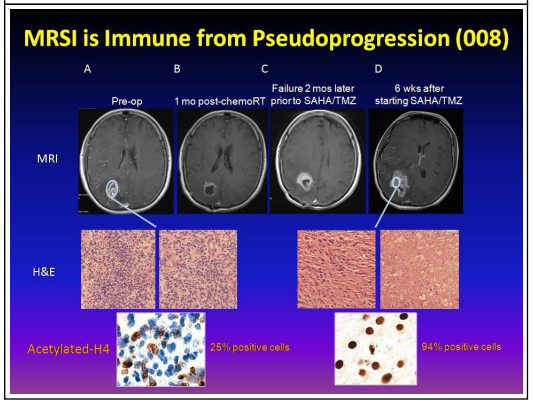
In our preclinical rodent model, MRS detects metabolic response/normalization to SAHA after only 3 days of treatment: alanine and lactate reduction and elevated myo-inositol, N-acetyl aspartate and creatine. This led to our clinical study of MRSI evaluation of metabolic responses of recurrent GBMs to SAHA and temozolomide. After only 7 days of SAHA treatment, MRSI can distinguish metabolic responders from non-responders by calculation of an index of normalization/restoration of tumor metabolites towards normal brain-like metabolism.





Our initial cohort (n=7) consists of 3 metabolic responders and 4 metabolic non-responders with highly significant differences in their change in metabolite levels ($p < 0.001$).





Learning Objectives

By the conclusion of this session, participants should be able to: 1) describe the importance of epigenetic modifications in tumorigenesis, 2) understand the metabolites measurable with magnetic resonance spectroscopic imaging and, 3) ascertain the value of early detection of tumor therapy effect by vorinostat as a model for this technique.

Conclusions

Our results provide insight into the mechanisms by which HDACi exerts its effect on GBMs. Tumor cells are known to have altered biosynthetic needs and cellular metabolism. MRSI results suggest HDACi may induce redifferentiation in tumors by targeting tumor metabolism. Thus, MRSI measurement of metabolism is a novel modality to predict response to HDACi-containing combination therapy in GBM. More importantly, this study serves as a demonstration project for early detection of treatment effect in glioblastoma using this modality.

References

Wei, L, Hong, S., Yoon, Y., Hwang, S.N., Park, J.C., Zhang, Z, Olson, J.J., Hu, X.P., and Shim, H. (2012) Early prediction of response to Vorinostat in an orthotopic glioma rat model. NMR in Biomedicine. Feb 2. DOI: 10.1002/nbm.2776 [Epub ahead of print]. PMID: 22302519

Acknowledgement

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