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Case Report

CASE REPORT

Remarkable response of a patient with secondary glioblastoma to a histone deacetylase inhibitor

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Abstract

Secondary glioblastoma is a rare brain tumor characterized by a mutation in isocitrate dehydrogenase, which is reported to lead to epigenetic modification. Patients with secondary glioblastoma experience poor survival and quality-of-life outcomes due to the disease's aggressiveness and a lack of targeted therapies. In this report, a patient with a secondary glioblastoma was treated with a histone deacetylase inhibitor, an epigenetic drug with potent anti-inflammatory properties, in addition to the standard regimen. The patient showed very favorable survival and quality-of-life measures, and a restoration of several neuro-metabolites as measured by spectroscopic magnetic resonance imaging.

INTRODUCTION

Glioblastomas can arise either as *de novo* primary tumors or as secondary tumors, which transition from lower grade gliomas into this grade IV histology [1]. Secondary glioblastomas commonly harbor a mutation of isocitrate dehydrogenase 1 (IDH1), which leads to the enzymatic conversion of α-ketoglutarate to 2-hydroxyglutarate (2-HG) [2]. The accumulation of 2-HG has several downstream effects due to its competitive inhibition of α-ketoglutarate-dependent enzymes, including epigenetic modification. Histone deacetylase inhibitors (HDACis) are a class of molecules that have a variety of antitumor and anti-inflammatory effects because HDACis also lead to downstream histone modification, HDACi may counter the effects of accumulated 2-HG in IDH1-mutant (IDH1mut) tumors. We recently showed that belinostat, an HDACi with good blood-brain barrier penetration, was effective in reducing tumor burden and improving behavior in an orthotopic rat model [3]. In this report, we present a patient with an IDH1mut secondary glioblastoma treated with belinostat alongside standard chemoradiation.

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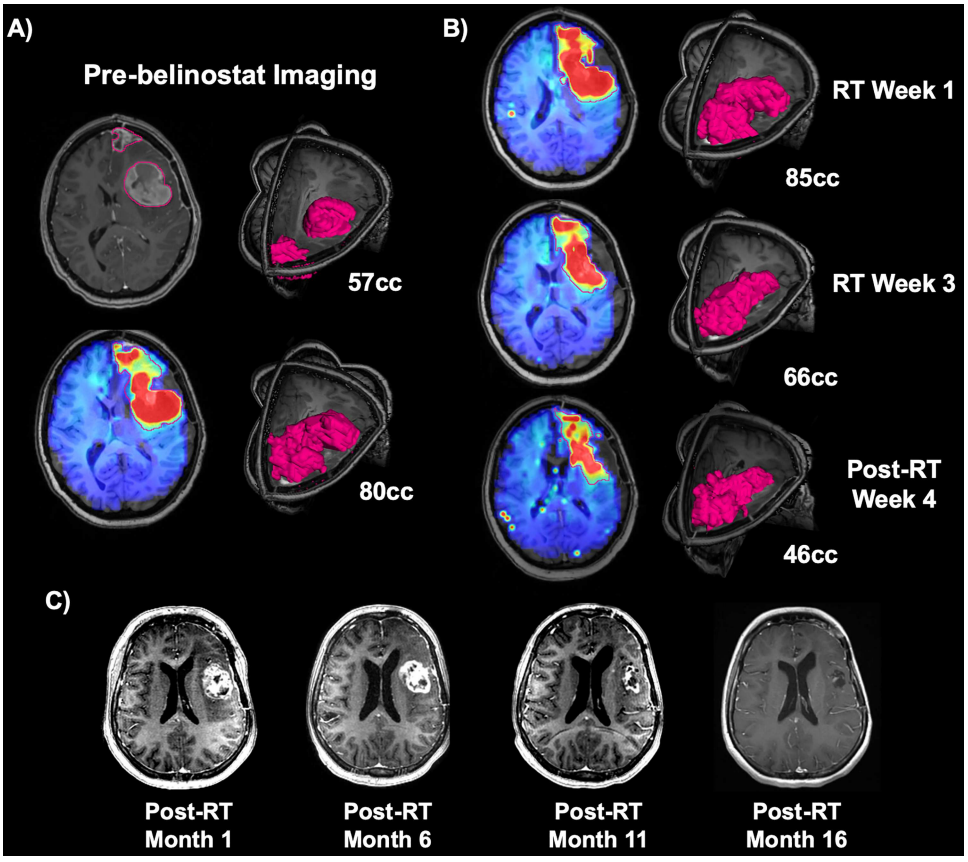


Figure 1: Imaging changes during therapy and the follow-up period. (**A**) shows a comparison of the standard T1w MRI and spectroscopic MRI lesions post-surgery but before chemoradiation. (**B**) shows the metabolite response during the course of therapy as measured by the Cho/NAA signal. (**C**) shows longitudinal T1w MRI scans for 16 months post-RT.

CASE REPORT

A 27-year-old woman presented with a 4-week history of left-sided headache and a 2-day history of nausea and blurry vision in the left eye. Magnetic resonance imaging (MRI) with and without contrast revealed an enhancing mass along the left Sylvian fissure and an adjacent non-enhancing mass in the left superior frontal gyrus. She underwent subtotal resection of the enhancing mass and histological analysis of the tissue showed IDH1mut (R132H) glioblastoma. Biopsies of the non-enhancing region revealed infiltrating astrocytes of a lower grade and were separately assessed for copy number variation analysis. MGMT (06-methylguanine-DNA methyltransferase) promoter methylation was negative and 1p19q was intact in both masses. A clinical diagnosis of secondary glioblastoma was made.

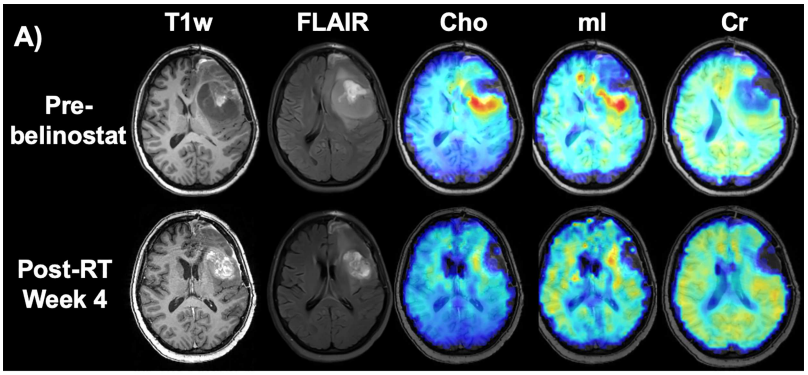
She consented and enrolled in a pilot study assessing the use of belinostat in addition to the standard chemoradiation regimen (NCT02137759), which consists of temozolomide (TMZ) (150–200 mg/m^2) concurrent with 60 Gy of radiation therapy (RT) over 6 weeks, followed by adjuvant TMZ for 1 year. She received intravenous doses of 500 mg/m^2/day belinostat for 5 days 1 week prior to RT and two additional 5-day cycles at 3-week intervals RT.

She underwent 3D spectroscopic MRI, which measures endogenous tissue metabolite activity and was used for monitoring metabolic response of chemoradiation [4]. Spectroscopic MRI scans were acquired at four time points: pre-belinostat, at the start of RT, at week 3 of RT and 4-weeks post-RT. Heatmaps of the metabolites choline (Cho), creatine (Cr), NAA, myo-inositol (mI) and Cho/NAA were generated. To assess distributions of metabolic activity, voxels were partitioned by lobe into gray matter and white matter and the lobar gray-to-white matter ratios of each metabolite were calculated [5]. For comparison, the same analyses were performed on a cohort of three healthy women aged 27–29 scanned at our institution and on a published cohort of normal subjects [5].

For neurocognitive assessment, our patient underwent the Hopkins Verbal Learning Test-Revised (HVLT-R) [6], trail making test parts A and B [7], Controlled Oral Word Association Test (COWAT) [8], MD Anderson Symptom Inventory Brain Tumor module (MDASI-BT) [9] and European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaires QLQ-C30 and QLC-BN20 [10].

Figure 1A shows the pre-belinostat imaging for this patient; the Cho/NAA heatmap revealed a larger area of hyperactivity that includes two separate tumor foci on standard imaging and the interconnecting region. Figure 1B shows the reduced size of Cho/NAA abnormality as the patient underwent chemoradiation. She continued to undergo bimonthly MRI to monitor for disease recurrence (Fig. 1C), and had stable disease for 16 months, when a distant recurrence was detected.

Figure 2A compares the mapping abnormally elevated metabolites at baseline and post-RT. At 1-month post-RT, the elevated levels were partially normalized, alongside a marked decrease in tumor size and mass effect. Figure 2B shows the



B) **Right Temporal Lobe GM/WM**

	Cho	Cr	ml
Pre-belinostat	0.70	1.10	0.81
Post-RT Week 4	0.90	1.34	1.03
Normal cohort (n=3)	0.84 ± 0.20	1.35 ± 0.10	1.17 ± 0.20
Maudsley et al (n=44)	0.90 ± 0.14	1.34 ± 0.13	--

Figure 2: Restoration of metabolic hyperactivity toward normal. (**A**) shows spectroscopic MRI measurements of Cho, mI and Cr prior to chemoradiation and 4 weeks after RT. (**B**) shows the grey-to-white matter ratios of metabolites in the right temporal lobe, a contralateral normal-appearing area, for this patient at baseline and post-RT week 4 in comparison with values from normal subjects.

Table 1: Summary of tests of neurocognition

Test	Baseline	1mo Post-RT	6mos Post-RT	12mos Post-RT	18mos Post-RT	Direction	*P*-value
HVLT-R total recall	4	10	10	27	27	Improved	0.021
HVLT-R delayed recall	1	2	3	10	12	Improved	**0.005**
Trail making part A	64	39	51	35	32	Improved	0.159
Trail making part B	235	145	250	105	92	Improved	0.188
COWAT	3	27	5	20	23	Improved	0.500
MDASI-BT	72	58	94	5	0	Improved	0.104
QLQ-C30	41	57	69	32	28	Improved	0.274
QLQ-BN20	35	38	37	26	23	Improved	0.028

Several tests of neurocognition were obtained from baseline up through 18 months post-RT. Two-sided *P*-values are provided and bolded if they reached statistical significance at a Bonferroni-corrected α of 0.006.

grey-to-white matter ratio for the right temporal lobe, a region distant from the tumor foci, for this patient compared to healthy controls. At baseline, the ratios for all metabolites were reduced; at 1-month post-RT, the ratios increased toward normal levels.

Table 1 shows the results of the neurocognition tests from baseline through 18 months post-RT. A linear regression was performed for each test, and the Wald test with the null hypothesis that the slope of linear regression is zero was performed using the SciPy library. All tests showed a consistent trend toward improvement over the patient's disease course.

DISCUSSION

HDACis are epigenetic drugs that may play a targeted role in patients with IDH1mut tumors. In this report, we present the single subject from a pilot study with an IDH1mut secondary glioblastoma who was treated with HDACi belinostat.

At baseline, spectroscopic MRI revealed a region of metabolic abnormality that spatially corresponded to the primary and secondary foci of the tumor, but also included the tissue between the two foci. Based on previous imaging-histological correlation [4], high Cho/NAA specifically and sensitively identifies the presence of tumor cells and provides insight into the underlying pathology of infiltration between the two foci on standard imaging.

At baseline, metabolites in the contralateral hemisphere, particularly in the right temporal lobe, showed decreased grey-to-white matter ratios compared to normal subjects, providing imaging evidence that there is altered metabolism in apparently healthy tissue (Fig. 1D). Paracrine signaling from and migration of tumor cells can lead to the activation of inflammatory responses distant from the primary tumor, and it is plausible that the altered metabolism in the contralateral hemisphere is due to this effect. This patient was observed to have restoration of metabolism in the contralateral hemisphere after treatment, with grey-to-white matter ratios comparable with health controls. While this effect could be due in part to reduced tumor burden, belinostat may play a role in further restoring normal metabolism via inhibiting epigenetic modification of 2-HG.

Finally, HDACi have been shown to improve mood and activity in animal models. This patient had a consistent improvement in neurocognition across all testing instruments over 18 months.

These findings suggest that the combination of an HDACi with chemoradiation may be beneficial for patients with a secondary glioblastoma. Additional research is necessary to assess the potential of HDACi therapy, and due to the relatively low incidence of secondary glioblastoma, we encourage the evaluation of such therapies in a multi-institutional study.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to report.

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ETHICAL APPROVAL

The design and execution of all work in this report was approved by the Institutional Review Board of Emory University. No identifiable information is presented in this report.

CONSENT

Consent obtained from the patient and available on request.

GUARANTOR

Hyunsuk Shim and Hui-Kuo Shu guarantee for the accuracy of this report.

REFERENCES

1. Ohgaki H, Kleihues P. Genetic pathways to primary and secondary glioblastoma. *Am J Pathol* 2007;**170**:1445–53.
2. Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, *et al*. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature* 2009;**462**:739–44.
3. Gurbani SS, Yoon Y, Weinberg BD, Salgado E, Press RH, Cordova JS, *et al*. Assessing treatment response of glioblastoma to an HDAC inhibitor using whole-brain spectroscopic MRI. *Tomography* 2019;**5**:53–60.
4. Cordova JS, Shu H-KG, Liang Z, Gurbani SS, LAD C, Holder CA, *et al*. Whole-brain spectroscopic MRI biomarkers identify infiltrating margins in glioblastoma patients. *Neuro Oncol* 2016;**18**:1180–9.
5. Maudsley AA, Domenig C, Govind V, Darkazanli A, Studholme C, Arheart K, *et al*. Mapping of brain metabolite distributions by volumetric proton MR spectroscopic imaging (MRSI). *Magn Reson Med* 2009;**61**:548–59.
6. Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins verbal learning test–revised: normative data and analysis of inter-form and test-retest reliability. *Clin Neuropsychol* 1998;**12**:43–55.
7. Reitan RM. Validity of the trail making test as an indicator of organic brain damage. *Percept Mot Skills* 1958;**8**: 271–6.
8. Ruff RM, Light RH, Parker SB, Levin HS. Benton controlled oral word association test: reliability and updated norms. *Arch Clin Neuropsychol* 1996;**11**:329–38.
9. Armstrong TS, Mendoza T, Gring I, Coco C, Cohen MZ, Eriksen L, *et al*. Validation of the MD Anderson symptom inventory brain tumor module (MDASI-BT). *J Neurooncol* 2006;**80**: 27–35.
10. Taphoorn MJB, Claassens L, Aaronson NK, Coens C, Mauer M, Osoba D, *et al*. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. *Eur J Cancer* 2010;**46**: 1033–40.