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RESEARCH ARTICLE

Impact of Slow- Infusion (Metronomic) 2-Deoxy-D-Glucose in Treatment of Refractory Patient of Gliobalstoma Multiforme

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Abstract

Glucose, an energy source for cells, also forms the backbone for the creation of ribose and deoxyribose, vital for RNA and DNA synthesis, and is key to the development of necessary lipids and specific amino acids for cell growth. It has been observed that amount of glucose usage corresponds with heightened malignancy, poor prognosis, and increased treatment resistance in cancer cells. It has been observed that modulation of glucose flux and energy supply to tumor cells leads to better cancer control. An innovative method to is the use of 2-deoxy-D-glucose (2-DG), it's a glucose molecule which has the 2-hydroxyl group replaced by hydrogen. It enters tumor cells preferentially through the same glucose transporters. Once inside, it gets phosphorylated by hexokinase to become 2-deoxy-d-glucose-6-phosphate (2-DG-6-P) which halts further glucose metabolism. This disruption severely depletes ATP in hypoxic tumor cells relying on glycolysis for energy, causing cell death. In areas with ample oxygen where fats and proteins serve as energy substitutes, ATP depletion is less acute, yet 2-DG administration curtails protein translation, hindering proteins vital for cell growth and duplication. 2-DG, also acting as a mannose mimetic, disrupts N-linked glycosylation and induces endoplasmic reticulum (ER) stress, which has shown to inhibit tumor cells' growth. Infusing 2-DG at low doses or metronomically is suggested to enhance cancer control. This case study shows substantial improvements in both radiological outcomes and clinical parameters in a Glioblastoma Multiforme; Grade IV patient by incorporating low dose metronomic 2-DG infusion into the treatment. The patient had undergone surgery followed by radiation and was on Temozolomide therapy. 2-DG disrupts cancer cells' energy metabolism significantly, making them more susceptible to cytotoxic drugs like doxorubicin, cisplatin, and gemcitabine, enhancing radiotherapy effects, particularly in Glioblastoma Multiforme.Malignant gliomas, some of the most resistant tumors, are incredibly heterogeneous with multiple hypoxic regions. 2-DG, due to its ability to penetrate the blood-brain barrier (BBB) and starve hypoxic cancer cells, holds significant potential in glioma treatments.

Overwhelming evidence from PET scans makes it clear that cells undergo a fundamental change in metabolizing glucose when they transform from normal to malignant, confirming data and hypotheses originally presented by Warburg in the 1920s.[1] Studies with carbon-13 labelled glucose have shown that, in addition to supplying energy to a cell, the glucose skeleton is used as a building block to produce ribose and deoxyribose necessary for RNA and DNA synthesis, as well as lipids and certain amino acids required for cell growth.[2] A tumor cell, being continuously driven through the cell cycle by oncogenes, must have a mechanism (increased glucose uptake) by which to procure the necessary precursors, as well as energy, required for rapid cell growth and division. It is now understood that the major genes driving carcinogenesis (oncogenes and loss of suppressors) are also responsible for increasing the uptake and metabolism of glucose.[2] Additionally, glucose usage has been shown to correlate with the degree of malignancy, poor prognosis, and conferring resistance to treatment.[3,4] Therefore, several approaches to modulate glucose flux and energy supply are being investigated and tried to improve disease outcome.

One major approach is the use of the glycolytic inhibitor, 2-deoxy-D-glucose (2-DG), which is well-suited to take advantage of increased glucose metabolism, a common trait inherent in tumors. Using the same transporters as glucose, 2-DG preferentially enters a tumor cell and is phosphorylated by hexokinase to 2-deoxy-d-glucose-6-phosphate (2-DG-6-P). However, unlike glucose, 2-DG-6-P cannot be further metabolized by phosphoglucose isomerase (PGI) to the 5-carbon ring structure, fructose-6-phosphate, the next metabolite in glycolysis.[5] Thus, accumulation of 2-DG-6-P within the cell leads to allosteric and competitive inhibition of hexokinase and isomerase, respectively, essentially shutting down further metabolism of glucose. In hypoxic tumor cells, this results in severe ATP depletion and cell death.[5] In areas within a tumor that receive enough oxygen, ATP depletion is less severe (as fats and proteins can act as energy sources), administering 2-DG leads to inhibition of protein translation through mTOR and subsequent blockage of its downstream kinase, p70S6K. This results in growth arrest by shutting down the proteins necessary for replication, i.e., cyclin D1.[5]

Alternatively, growth inhibition can occur due to 2-DG's ability to act as a mannose mimetic, interfering with N-linked glycosylation.[6] As a consequence, ER stress is induced, activating the UPR signal transducer PERK, which phosphorylates the mRNA translation initiation factor eIF2α. This results in the lowering of cyclin D1 levels, blocking the cell cycle and growth.[6] Thus, 2-DG's activity as a glycolytic inhibitor inducing energy stress, and as an inhibitor of N-linked glycosylation leading to ER stress, at clinically achievable doses, has been shown to block cell growth of many tumor cell types.[5]

With these mechanistic understandings, along with preclinical tumor animal model studies, toxicology, and pharmacokinetics, a Phase I clinical trial showed that although 2-DG was well-tolerated in patients, drinking it once per day induced an insulin response.[7] Under these conditions, it was hypothesized that 2-DG, much like glucose, would be redirected to muscle and fat tissue and away from the tumor. Additionally, at a high enough level, 2-DG will be absorbed by the liver, thereby reducing its tumor concentration.

Based on these considerations, experiments in a human melanoma xenograft mouse model, where 2-DG was delivered via a slow-release (ALZET) pump (41µg/ml/hr, a dose far below that which would induce an insulin response or be absorbed by the liver), proved to be effective in lowering tumor volume burden.[8] Moreover, the total dose per week, 462mg/kg, delivered by this method is 3 times lower than the total dose previously shown to have activity when animals were treated by IP injection 3x/week,[8] suggesting low dose (metronomic) infusion of 2-DG to be effective in augmenting cancer control.

Here, a case study is presented of a patient with treatment-resistant high-grade Glioblastoma Multiforme, where slow-drip 2-deoxy-D-glucose (2-DG) was added to standard treatment.

Case Report

After presenting with right-side weakness, a 55-year-old male patient underwent a left craniotomy for a left parietal lobe tumor in October 2020. The histopathology suggested Glioblastoma Multiforme; Grade IV. Post-surgery, 50 Gy radiation was completed in December 2020, which was followed by three cycles of the chemotherapeutic Temozolomide, commonly used for this disease.

An April 2021 scan (DOPA PET MRI) showed a decrease in the size of the previous lesion but increased uptake of choline along the margins. A June 2021 scan suggested a mild increase in the size of the left parietal lobe lesion as compared to that observed in April, accompanied by marked peri-lesion edema extending up to the internal and external capsule. By January 2022 (Figure 1), the lesion size had increased further, showing areas of high perfusion and central necrosis. The scan also revealed an increase in

internal FLAIR, suggestive of lesions in proximity to CSF, such as cerebral cortical lesions.

At this time, the patient's health status had deteriorated with a decrease in cognitive function, increased right-side weakness, and the onset of seizures. A 48-hour metronomic (slow-drip) infusion of 1 gram/100 ml 2-DG was begun, given once a week between the cycles of Temozolomide, which consisted of 5 days of Temozolomide every three weeks. Within five months, by June 2022 (Figure 2), the patient's clinical condition clearly improved; his motor power increased and the seizures stopped. A scan suggested a reduction of FLAIR with the size of the lesion remaining the same.

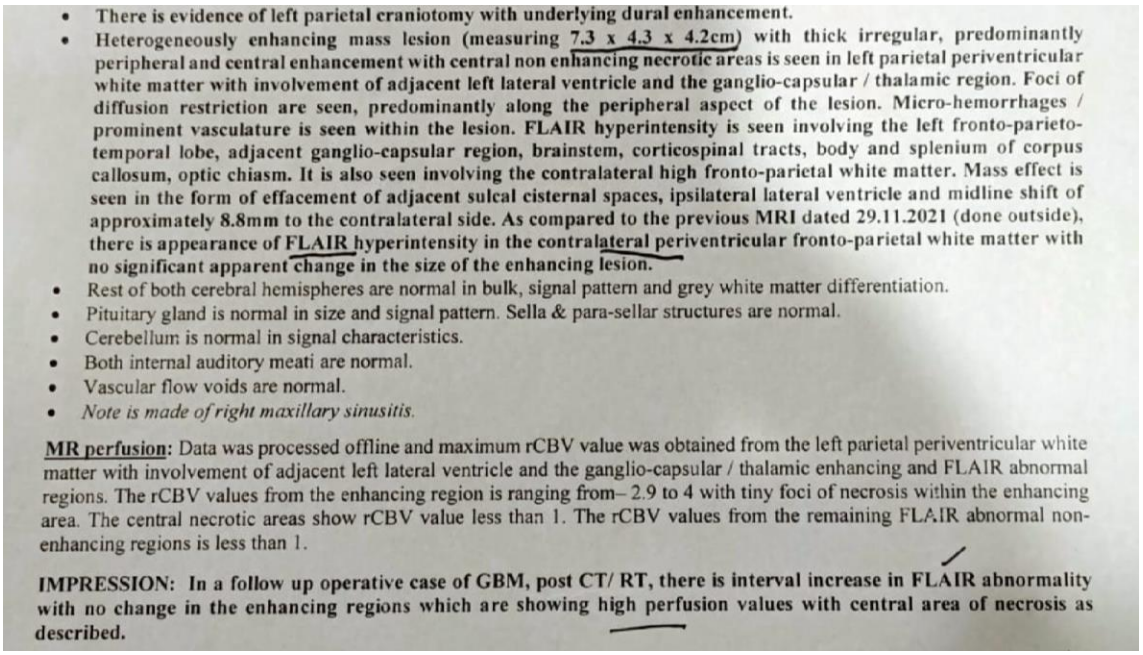
Temozolomide was stopped in November 2022, and since then, the patient is only being treated with weekly 2-DG. The most recent MRI in March 2023 showed neither disease progression nor an increase in FLAIR.

Discussion

Chemotherapy and radiation, standard anti-cancer treatments, primarily interfere with the dividing machinery of cells, mainly DNA and RNA. Unfortunately, a large majority of patients treated with these modalities undergo recurrence. Apart from factors such as stage, grade, and site which influence treatment response, another principal reason for recurrence is the presence of a population of cancer stem cells within every solid tumor. These cells are not actively dividing and are therefore resistant to therapy. Thus, while cancer treatment may initially shrink the tumor by killing the actively replicating cells, the slow or non-replicating cells remain, serving as a source for further tumor growth.

As a tumor increases in size, neo-angiogenesis can no longer keep up with cell proliferation, leading to areas of hypoxia. This condition is a major mechanism of resistance to cancer treatment, as it slows down tumor replication which is required for radiation and/or chemotherapy effectiveness.[9] As mentioned above, 2-DG blocks glycolysis, effectively targeting this hypoxic population of resistant cells. Moreover, the lack of oxygen leads to decreased production of reactive oxygen species, and consequently, reduced DNA damage with radiotherapy and/or chemotherapeutic cytotoxic agents that rely on it for their ability to kill cancer cells.[10-12]

Figure 1

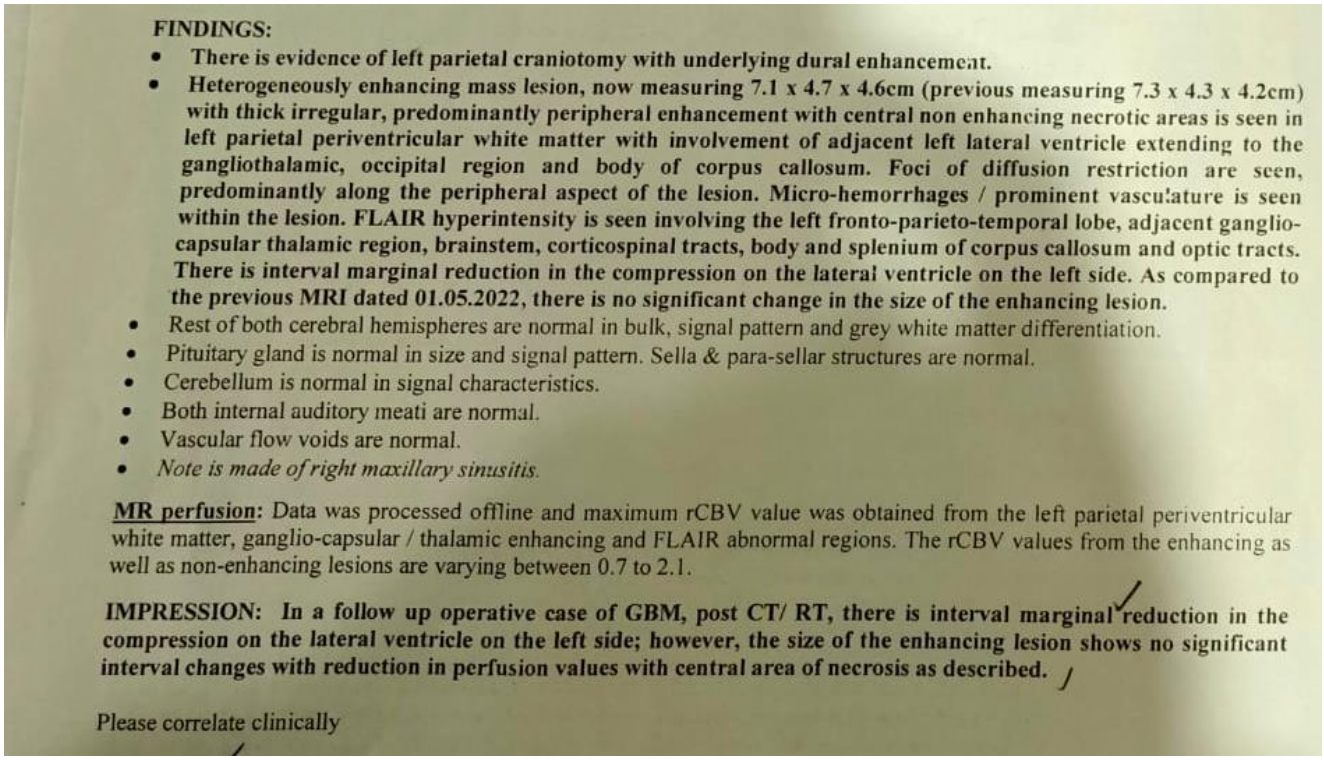


- There is evidence of left parietal craniotomy with underlying dural enhancement.
- Heterogeneously enhancing mass lesion (measuring 7.3 x 4.3 x 4.2cm) with thick irregular, predominantly peripheral and central enhancement with central non enhancing necrotic areas is seen in left parietal periventricular white matter with involvement of adjacent left lateral ventricle and the ganglio-capsular / thalamic region. Foci of diffusion restriction are seen, predominantly along the peripheral aspect of the lesion. Micro-hemorrhages / prominent vasculature is seen within the lesion. FLAIR hyperintensity is seen involving the left fronto-parieto-temporal lobe, adjacent ganglio-capsular region, brainstem, corticospinal tracts, body and splenium of corpus callosum, optic chiasm. It is also seen involving the contralateral high fronto-parietal white matter. Mass effect is seen in the form of effacement of adjacent sulcal cisternal spaces, ipsilateral lateral ventricle and midline shift of approximately 8.8mm to the contralateral side. As compared to the previous MRI dated 29.11.2021 (done outside), there is appearance of FLAIR hyperintensity in the contralateral periventricular fronto-parietal white matter with no significant apparent change in the size of the enhancing lesion.
- Rest of both cerebral hemispheres are normal in bulk, signal pattern and grey white matter differentiation.
- Pituitary gland is normal in size and signal pattern. Sella & para-sellar structures are normal.
- Cerebellum is normal in signal characteristics.
- Both internal auditory meati are normal.
- Vascular flow voids are normal.
- *Note is made of right maxillary sinusitis.*

MR perfusion: Data was processed offline and maximum rCBV value was obtained from the left parietal periventricular white matter with involvement of adjacent left lateral ventricle and the ganglio-capsular / thalamic enhancing and FLAIR abnormal regions. The rCBV values from the enhancing region is ranging from– 2.9 to 4 with tiny foci of necrosis within the enhancing area. The central necrotic areas show rCBV value less than 1. The rCBV values from the remaining FLAIR abnormal non-enhancing regions is less than 1.

IMPRESSION: In a follow up operative case of GBM, post CT/ RT, there is interval increase in FLAIR abnormality with no change in the enhancing regions which are showing high perfusion values with central area of necrosis as described.

Figure 2



FINDINGS:

- **There is evidence of left parietal craniotomy with underlying dural enhancement.**
- **Heterogeneously enhancing mass lesion, now measuring 7.1 x 4.7 x 4.6cm (previous measuring 7.3 x 4.3 x 4.2cm) with thick irregular, predominantly peripheral enhancement with central non enhancing necrotic areas is seen in left parietal periventricular white matter with involvement of adjacent left lateral ventricle extending to the gangliothalamic, occipital region and body of corpus callosum. Foci of diffusion restriction are seen, predominantly along the peripheral aspect of the lesion. Micro-hemorrhages / prominent vasculature is seen within the lesion. FLAIR hyperintensity is seen involving the left fronto-parieto-temporal lobe, adjacent ganglio-capsular thalamic region, brainstem, corticospinal tracts, body and splenium of corpus callosum and optic tracts. There is interval marginal reduction in the compression on the lateral ventricle on the left side. As compared to the previous MRI dated 01.05.2022, there is no significant change in the size of the enhancing lesion.**
- Rest of both cerebral hemispheres are normal in bulk, signal pattern and grey white matter differentiation.
- Pituitary gland is normal in size and signal pattern. Sella & para-sellar structures are normal.
- Cerebellum is normal in signal characteristics.
- Both internal auditory meati are normal.
- Vascular flow voids are normal.
- *Note is made of right maxillary sinusitis.*

MR perfusion: Data was processed offline and maximum rCBV value was obtained from the left parietal periventricular white matter, ganglio-capsular / thalamic enhancing and FLAIR abnormal regions. The rCBV values from the enhancing as well as non-enhancing lesions are varying between 0.7 to 2.1.

IMPRESSION: In a follow up operative case of GBM, post CT/ RT, there is interval marginal reduction in the compression on the lateral ventricle on the left side; however, the size of the enhancing lesion shows no significant interval changes with reduction in perfusion values with central area of necrosis as described.

Please correlate clinically

Importantly, hypoxic areas harbor cancer stem cells resistant to radiation and standard chemotherapy. In a transgenic mouse model of retinoblastoma, these cells were shown to be selectively targeted and killed by 2-DG.[13] Additionally, Valera et al.[14] found 2-DG to sensitize cancer cells to cytotoxic drugs such as doxorubicin, cisplatin, and gemcitabine. The radiosensitizing effect of adjuvant 2-DG in radiotherapy has been demonstrated in breast, cervical, lung, and especially in GBM cancers.[9,15-17]

Malignant gliomas are among the most treatment-resistant tumors. They are heterogeneous, containing multiple regions of hypoxic and nonproliferating cell subpopulations. Cancer stem cells present in hypoxic niches are known to be a major cause of the progression, metastasis, and relapse in this disease. The ability of 2-DG to penetrate the BBB (blood-brain barrier) easily[18] and its role in starving the hypoxic cancer cell make it particularly useful in treating gliomas.

However, as mentioned above, a bolus dose delivery of 2-DG leading to an insulin response reduces its effectiveness. Here we provide evidence that in a patient continuously treated with a low dose of 2-DG (far below that which would induce an insulin response), in combination with standard chemotherapy, leads to cessation of seizures presumably caused by the progression of glioblastoma as well as a reduction in FLAIR. These data add to several others (personal communication) which indicate that metronomic or slow-drip low-dose delivery of 2-DG in patients with a variety of different cancer types reduces tumor size and tumor-associated symptoms.

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Conflicts of Interest

None

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None

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