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Extensive Shrinkage and Long-term Stable Disease in a Teenage Female Patient With High-grade Glioma Treated With Temozolomide and Radiation in Combination With Oral Recombinant Methioninase and a Low-methionine Diet

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Abstract. *Background/Aim: Gliomas are the most common and recalcitrant malignant primary brain tumors. All cancer types are addicted to methionine, which is a fundamental and general hallmark of cancer known as the Hoffman effect. Particularly glioma cells exhibit methionine addiction. Because of methionine addiction, [^{11}C]-methionine positron emission tomography (MET-PET) is widely used for glioma imaging in clinical practice, which can monitor the extent of methionine addiction. Methionine restriction including recombinant methioninase (rMETase) and a low-methionine diet, has shown high efficacy in preclinical models of gliomas, especially in combination with chemotherapy. The aim of the present study was to determine the efficacy of methionine restriction with oral rMETase (o-rMETase) and a low-methionine diet, combined with radiation and temozolomide (TMZ), on a teenage female patient with high-grade glioma. Case Report: A 16-year-old girl was diagnosed with high-grade glioma. Magnetic resonance imaging (MRI) showed a left temporal-lobe tumor with compression to the left lateral ventricle and narrowing of sulci in the left temporal lobe. After the start of methionine restriction with o-rMETase and a low-methionine diet, along with TMZ combined with radiotherapy, the tumor size shrunk at least 60%, with improvement in the left lateral ventricle and sulci. The patient's condition remains stable for 19 months without severe adverse effects. Conclusion: Methionine restriction consisting of o-rMETase and a low-methionine diet, in combination with radiation and TMZ as first-line chemotherapy, were highly effective in a patient with high-grade glioma.*

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Gliomas are the most common and recalcitrant primary brain and other nervous-system malignant tumors in the United States (1). Although multidisciplinary therapies such as surgical resection, radiation and chemotherapy have been introduced, gliomas are prone to recurrence and have a very poor prognosis (2). Especially for high grade glioma, the 5-year survival rate is 6.7% (1) and the average survival is 9 months (3).

All cancer types are addicted to methionine, which is a fundamental and general hallmark of cancer known as the Hoffman effect (4-7). Methionine addiction is at least partly due to excess transmethylation in cancer cells, leading to a much higher demand for external methionine in comparison to normal cells (4, 8-12). Therefore, cancer cells are incapable of surviving without exogenous methionine, despite their high endogenous production of methionine (4, 10-12).

Glioma cells are particularly methionine addicted. [^{11}C]-methionine positron emission tomography (MET-PET) is used for diagnosis (13, 14), treatment (15, 16) and to estimate prognosis (17, 18) in glioma. MET-PET yields a stronger and more accurate signal than [^{18}F]-deoxyglucose PET (FDG-PET), as gliomas are more methionine addicted than glucose addicted (19). Moreover, a reduced intake of methionine seen on MET-PET is linked to a better prognosis of malignant glioma (20, 21).

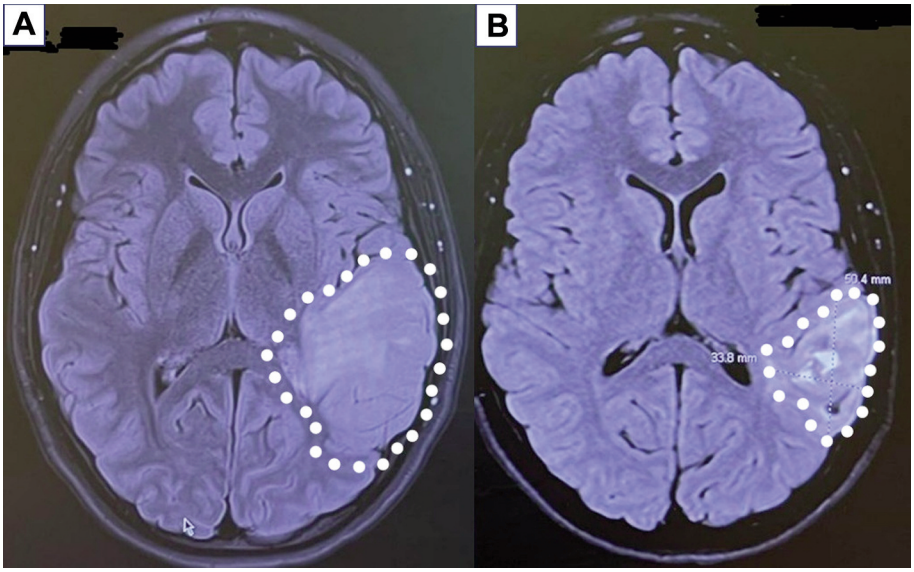

Figure 1. *MRI images of the brain of a 16-year-old girl with high grade glioma. A) The tumor was located in the left temporal lobe with compression of the left lateral ventricle and narrowing of left temporal lobe sulci before the start of treatment in July 2022. The patient began methionine restriction with o-rMETase and a low-methionine diet along with TMZ (75 mg/m^2) combined with radiotherapy in August 2022. After completion of radiotherapy, the dose of TMZ was increased to 150 mg/m^3. B) The tumor shrunk with improvement of the left lateral ventricle and left temporal lobe sulci in March 2023. o-rMETase: Oral recombinant methioninase; TMZ: temozolomide.*

Temozolomide (TMZ) is an oral alkylating agent used as first-line chemotherapy for glioma (22). TMZ functions by methylating DNA resulting in DNA damage, causing cell-cycle arrest in the G_2/M phase and death of glioma cells (23). However, the improvement of overall survival by TMZ is limited (24).

Our laboratory has developed recombinant methioninase (rMETase) for methionine restriction (25). When administered orally (o-rMETase), this enzyme breaks down methionine in the gut, leading to a reduction in methionine levels in the circulation and in tumors (26). Since, methionine restriction, including rMETase, selectively arrests the cell cycle of cancer cells in the late-S/G_2 phase (27, 28), alkylating drugs showed a synergistic effect when combined with methionine restriction in mouse models of glioblastoma, since they are methionine addicted (29-35).

In the present case report, a 16-year-old girl with high-grade glioma treated with radiation and temozolomide combined with oral rMETase (o-rMETase) and a low-methionine diet, demonstrated extensive tumor shrinkage and subsequent stable disease for 19 months, thus far.

Materials and Methods

Production and formulation of rMETase. rMETase was produced by fermenting recombinant *Escherichia coli* transformed with the *methioninase* gene from *Pseudomonas putida*. The purification of methioninase involved a high-yield method that had a heat step at 60˚C, polyethylene glycol precipitation, and ion-exchange column chromatography using diethylaminoethyl (DEAE)-Sepharose FF (36, 37).

Methionine restriction and o-rMETase administration. The patient stayed on a methionine restricted diet, following the Nutritional Oncology Research Institute (NORI) protocol (38). This procedure recommends less than 2 mg/kg body weight methionine intake per day. o-rMETase was administered orally twice a day 30 min after each meal at a dose of 250 units, as a supplement.

Case Report

A 16-year-old girl was diagnosed with high-grade glioma in July 2022. Magnetic resonance imaging (MRI) showed a left temporal lobe tumor with compression to the left lateral ventricle and narrowing of sulci in the left temporal lobe (Figure 1A).

The patient began methionine restriction with o-rMETase and a low-methionine diet along with TMZ (75 mg/m^2) combined with radiotherapy in August 2022. After she completed radiotherapy in October 2022, the dose of TMZ was increased to 150 mg/m^2.

An MRI showed an extensive reduction in the size of the tumor, along with improvement in the lateral ventricles and sulci by nine months after the start of treatment (Figure 1B). The tumor shrunk at least 60% by nine months of treatment with radiation and TMZ combined with o-rMETase and a low-methionine diet and is currently stable after 19 months (Figure 2). This allows her to maintain the current combination

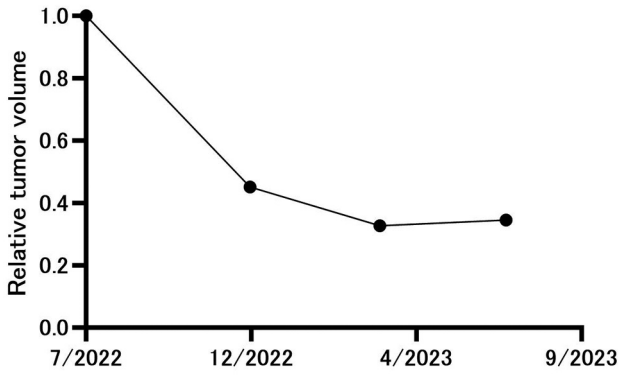

Figure 2. *Relative-brain tumor volume over time of treatment. The patient began methionine restriction with o-rMETase, and a low-methionine diet along with TMZ (75 mg/m^2) combined with radiotherapy in August 2022. After completion of radiotherapy, the dose of TMZ was increased to 150 mg/m^3. The tumor volume at diagnosis in July 2022 was designated as 1. o-rMETase: Oral recombinant methioninase; TMZ: temozolomide.*

treatment of TMZ and o-rMETase and a low-methionine diet without severe adverse effects.

Discussion

This is the first clinical report of combining TMZ and methionine restriction, comprising oral rMETase and a low-methionine diet, on a patient with high-grade glioma.

In a clinical trial, the median survival was 14.6 months among high-grade glioma patients treated with radiation and TMZ (24). However, patients who participate in clinical trials usually have better performance status (PS) and often more stable disease than the general population of high-grade glioma. The median survival in the general population of high-grade glioma was reported to be 9 months (3). It is noteworthy that the patient in the present study has maintained a good PS for 19 months since diagnosis.

Since gliomas are heterogeneous and resistant to all modalities of standard treatment including surgery, radiation and TMZ, which has not changed for 20 years despite many attempts at implementing new treatments (39). An effective treatment is urgently required.

Methionine addiction is a fundamental and general hallmark of all cancer types, including glioma, as seen in preclinical studies (29-35). Methionine restriction with rMETase and a low-methionine diet greatly enhanced the efficacy of an alkylating agent in mouse models of brain cancer (31, 32, 35).

Histone-methylation alteration in cancer is linked to methionine addiction (8, 40, 47). S-adenosylmethionine (SAM), the main metabolite of MET and universal methyl donor in the cell, contributes to the malignancy of cancer (10, 40). Suppressing SAM by methionine restriction inhibits glioma growth (41).

We first found that methionine restriction is synergistic with chemotherapy almost 40 years ago (42). Subsequently, a large amount of research has shown that there is synergy between methionine restriction, specifically with rMETase and/or a low-methionine diet, and all types of chemotherapy (43).

The present study suggests that methionine restriction is promising in combination with radiation and chemotherapy for high grade glioma. Methionine restriction does not involve the blood-brain barrier. Further clinical studies are necessary.

o-rMETase is effective as it targets the fundamental basis of cancer (4-12, 27, 28, 40, 44-57) and has shown potential efficacy in the clinic for other cancers including prostate cancer (58-60), colorectal cancer (61, 62), pancreatic cancer (63) and breast cancer (64).

Recent studies have suggested that MAT2A and histone methylation are therapeutic targets for diffuse midline gliomas and other cancers (65, 66). The present and previous results indicate that methionine addiction is a superior and safer target for gliomas and other cancers (4-10, 29-35, 40, 46-54).

Conflicts of Interest

The Authors declare no competing interests regarding this work.

Authors' Contributions

MS and RMH wrote the article. MS, QH, RM, KM, SM, BMK, NK, YI, AN, and RMH reviewed the article.

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