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Low-dose temozolomide combined with valproic acid in the treatment of an elderly patient with MGMT-methylated glioblastoma and multiple comorbidities: a case report

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Background: The prognosis for very elderly patients with glioblastoma (GBM) is extremely poor. For patients with a high tumor burden, multiple severe comorbidities, and poor physical condition, standard surgery and chemoradiotherapy are often poorly tolerated, and there is an urgent need for effective, low-toxicity palliative treatment options.

Case presentation: The patient is an 85-year-old man who presented with progressive speech difficulty. Imaging revealed a large left frontal lobe GBM measuring 6.4 cm × 6.0 cm with intratumoral hemorrhage. Molecular testing showed positive O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, wild-type IDH1/2, and negative BRAF V600E. The patient had multiple severe comorbidities, including epilepsy, congestive heart failure, type 2 diabetes mellitus, cerebral infarction, and severe malnutrition. The baseline Eastern Cooperative Oncology Group (ECOG) score was 4, and the Karnofsky Performance Status (KPS) score was 30; after systematic treatment, follow-up showed an ECOG score of 3 and a KPS score of 50. Treatment and outcome: Starting from 25 December 2024, palliative treatment was initiated with metronomic low-dose temozolomide (50 mg/day, continuous oral administration without dose reduction or interruption) combined with sodium valproate (0.4 g/dose, three times daily, administered via nasogastric tube). Concurrently, standard symptomatic and supportive treatments were given, including osmotic dehydration with mannitol and low-dose dexamethasone (corticosteroids). Because of the patient's critical condition and inability to be transported or undergo MRI, imaging efficacy evaluation was performed solely using head CT scans, and the MRI-RANO response criteria could not be applied. The regimen was well tolerated, with no myelosuppression or abnormal liver function. At the 3-month follow-up, serial head CT scans indicated stable disease without progression; ECOG and KPS scores showed significant improvement compared to baseline.

Conclusion: Low-dose metronomic temozolomide combined with sodium valproate is a safe and feasible palliative treatment strategy for very elderly GBM patients with MGMT promoter methylation, poor physical condition, and an inability to tolerate standard therapy. This study is a single-case report, and the conclusions have limitations, requiring validation through large-sample clinical studies.

KEYWORDS

elderly, glioblastoma, MGMT promoter methylation, palliative care, sodium valproate, temozolomide

1 Introduction

Glioblastoma (GBM, WHO grade IV) is the most malignant primary brain tumor in adults, with a peak incidence at ages 75–84. Elderly patients often have multiple severe comorbidities and poor performance status, making it difficult to tolerate the standard regimen of maximal safe resection combined with concurrent temozolomide chemoradiotherapy. Although short-course radiotherapy combined with temozolomide can improve survival in some elderly patients, palliative treatment remains the mainstay for those who are very elderly, have large tumors, or suffer from multiple organ dysfunction.

O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation is a key biomarker for predicting temozolomide efficacy and indicating a favorable prognosis. Valproic acid (VPA), a commonly used antiepileptic drug in clinical practice, also exhibits histone deacetylase inhibitor (HDACi) activity, which can epigenetically downregulate MGMT expression and enhance the anti-tumor activity of temozolomide. This article reports a case of an 85-year-old patient with MGMT promoter methylation-positive GBM treated with low-dose metronomic temozolomide combined with VPA, evaluating the safety and disease stabilization effect of this regimen.

2 Case report

2.1 Patient's basic information

The patient's full disease timeline is summarized in Table 1: On 28 May 2024, a routine head CT revealed an incidental low-density lesion in the left frontal lobe; on 18 November 2024, sudden speech difficulty and right limb tremors occurred; on 5 December 2024, neuroendoscopic biopsy was performed; on 13 December 2024, the patient was formally admitted; on 25 December 2024, systemic drug therapy was initiated; and regular follow-up continued until the last review on 5 March 2025.

An 85-year-old man was admitted on 13 December 2024, due to "intracranial mass discovered 15 days prior". On 18 November 2024, he experienced sudden speech difficulty and right limb tremors. Emergency head CT showed a mixed-density lesion in the left frontal lobe, suspected to be a tumor with hemorrhage. He was admitted to the neurosurgery department of our hospital and initially treated for cerebrovascular disease.

TABLE 1 Key timeline of patient diagnosis and treatment.

Examination/ treatment date	Key treatment content
28 May 2024	Incidental finding of a hypodense lesion in the frontal lobe on CT scan
18 November 2024	Sudden onset of aphasia and limb twitching; CT indicated a lesion with hemorrhage
5 December 2024	Neuroendoscopic biopsy + ICP monitoring implantation
13 December 2024	Formal hospitalization for treatment
25 December 2024	Initiation of palliative chemotherapy with temozolomide + valproic acid
14 February 2025	Follow-up head CT scan after 2 months of treatment
5 March 2025	Last follow-up: clinical and imaging review

On 5 December 2024, owing to the large tumor, severe edema, and high risk of brain herniation, neuroendoscopic biopsy combined with intracranial pressure (ICP) monitoring probe implantation was performed; postoperatively, ICP decreased from 28–32 mmHg to 15–20 mmHg. The relief of intracranial hypertension and neurological improvement after surgery were partially attributable to the decompressive effect of endoscopic surgery and cannot be entirely attributed to subsequent systemic anti-tumor drug efficacy.

Pathological results (10 December 2024) confirmed GBM, WHO grade IV; immunohistochemistry showed GFAP (focal +), vimentin (+), SOX-2 (+), S-100 (+), and Ki-67 index of approximately 30%. Typical pathological morphology and immunohistochemical findings are shown in Figures 1, 2.

Molecular testing revealed MGMT promoter methylation (+), while IDH1/2 mutation (−) and BRAFV600E (−) were not detected.

The patient had a history of epilepsy, grade 3 hypertension, congestive heart failure, type 2 diabetes mellitus, cerebral infarction, bilateral subclavian artery stenosis (stent implantation), deep vein thrombosis of the lower extremity, severe malnutrition, and other multiple serious comorbidities.

Baseline laboratory tests (December 2024, before treatment) revealed the following: complete blood count: white blood cells 6.86 $\times 10^9$/L, hemoglobin 149 g/L, and platelets 148 $\times 10^9$/L; liver and kidney function: alanine aminotransferase 21.1 U/L, aspartate

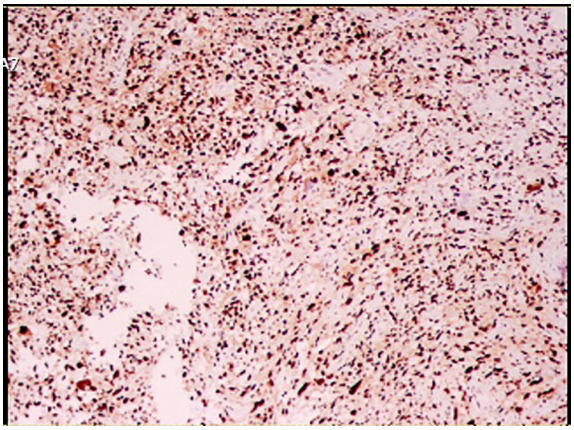


FIGURE 1
Immunohistochemical staining of glioblastoma (×200). Diffuse brownish positive expression in the cytoplasm of tumor cells indicates a glial-derived tumor, supporting the pathological diagnosis of glioblastoma.

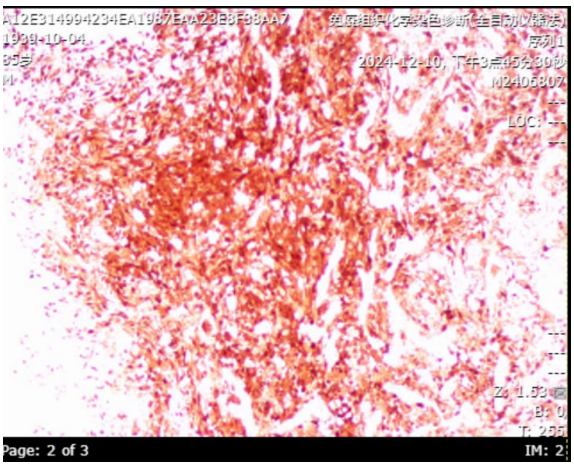


FIGURE 2
Ki-67 immunohistochemical staining (×200). Tumor cell nuclei show brown positive expression, with a Ki-67 proliferation index of approximately 30%, indicating a high proliferative activity of tumor cells, consistent with the pathological features of glioblastoma.

aminotransferase 19.0 U/L, albumin 34.6 g/L, creatinine 64.3 μmol/L, and blood urea nitrogen 8.59 mmol/L; and electrolytes: potassium 3.54 mmol/L, sodium 145.8 mmol/L, chloride 110.7 mmol/L, and blood sugar 5.51 mmol/L.

At baseline, the Eastern Cooperative Oncology Group (ECOG) score was 4 and the Karnofsky Performance Status (KPS) score was 30.

2.2 Physical examination and differential diagnosis at admission

The patient was admitted in December 2024. He was in a lethargic state and malnourished in appearance. His body temperature was 36.8°C, with pulse 99 beats/min, respiration 18 breaths/min, blood pressure 106/58 mmHg, and oxygen saturation 83%. Upon systemic examination, fine wet rales were heard in the left lower lung, suggesting a pulmonary infection. The abdomen was flat and soft without tenderness, with mild pitting edema present in both lower limbs. Neurological examination showed pupils were round and equal bilaterally, with a diameter of 2 mm and sluggish light reflexes. Cranial nerve examination was poorly cooperative. Limb muscle tone was normal, and muscle strength could not be accurately graded because of poor consciousness. Physiological reflexes were present, and pathological reflexes were not elicited.

Differential diagnosis: (1) Elderly cerebral infarction: The patient's CT findings in May 2024 resembled ischemic foci, with progressive enlargement and bleeding later, ruled out by pathological results; (2) Intracranial brain abscess: There was no persistent high fever or infectious blood profile, and postoperative pathology was not supportive. (3) Intracranial metastatic tumor: There was no history of systemic solid tumors, and pathology confirmed primary GBM.

Dynamic imaging changes: The patient's entire course of head CT dynamic evolution is shown in Figures 3–7, documenting the full process from initial diagnosis to follow-up.

28 May 2024 (incidental screening CT): A low-density lesion was seen in the left frontal lobe, initially suspected as cerebral infarction, with no significant mass effect.

18 November 2024 (symptom onset) CT: The left frontal lobe lesion was significantly enlarged, showing mixed hyperdensity with intratumoral bleeding, consistent with a neoplastic lesion.

5 December 2024 (post-biopsy) CT: A mixed-density mass was observed in the left frontal lobe (6.4 cm × 6.0 cm), with intratumoral bleeding and severe vasogenic edema, midline shift, and compression of ventricles.

14 February 2025 (2 months post-treatment) CT: The lesion size was stable, with bleeding partially absorbed and perilesional edema significantly reduced after hormone and dehydration therapy.

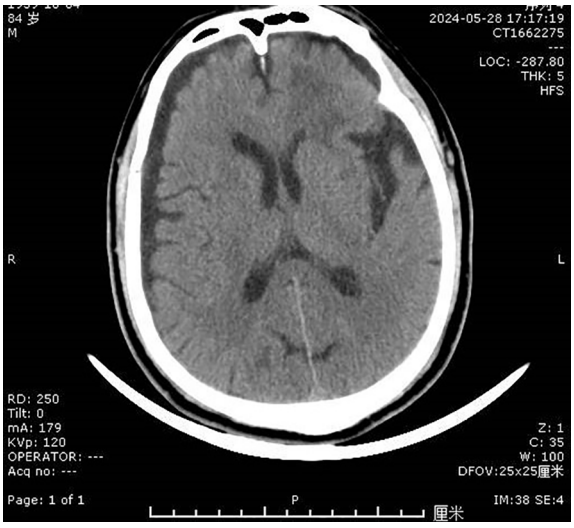


FIGURE 3
Head CT on 28 May 2024 (first abnormal). A low-density lesion was observed in the left frontal lobe, initially considered an ischemic change, with no significant mass effect.

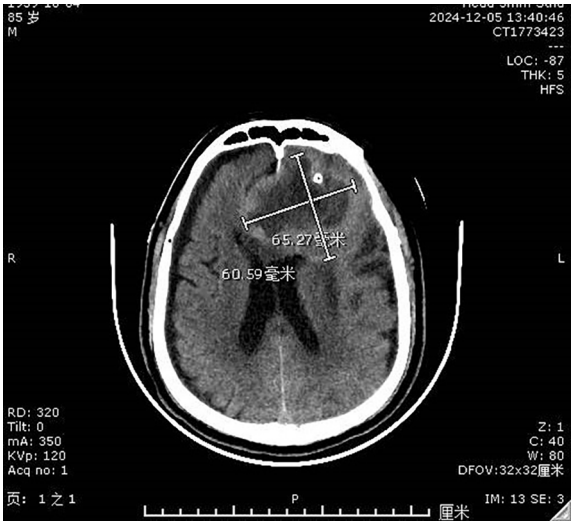


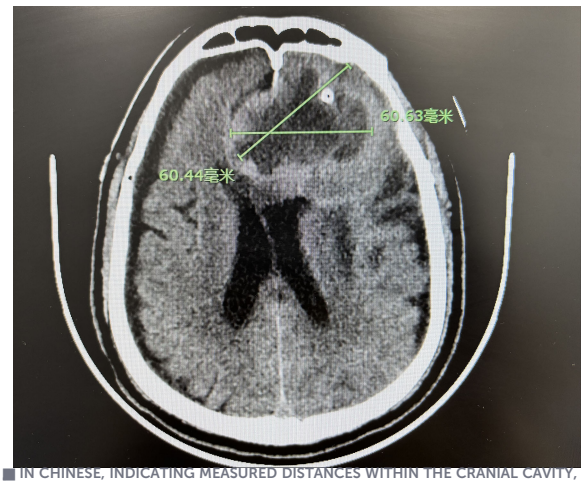
FIGURE 4
Head CT on 18 November 2024 (symptom onset). The lesion in the left frontal lobe had enlarged, with mixed hyperdensity with hemorrhage, highly suggestive of a neoplastic lesion.

5 March 2025 (last follow-up) CT: The lesion showed no progression, the edema was further reduced, and the patient's condition remained stable.

2.3 Treatment plan

After a multidisciplinary discussion, it was determined that the patient could not tolerate standard surgery and radiotherapy. Palliative care was initiated on 25 December 2024.

For temozolomide, 50 mg/day was administered via gastric tube, as a continuous metronomic dosing regimen without any drug discontinuation, dose reduction, or treatment interruption from the start of medication to the end of follow-up.



■ IN CHINESE, INDICATING MEASURED DISTANCES WITHIN THE CRANIAL CAVITY, LIKELY FOR DIAGNOSTIC PURPOSES.

FIGURE 5
Postoperative cranial CT on 5 December 2024. There was a large space-occupying lesion in the left frontal lobe (6.4 cm × 6.0 cm), accompanied by hemorrhage, severe edema, and compression of the cerebral ventricles■ in Chinese, indicating measured distances within the cranial cavity, likely for diagnostic purposes.

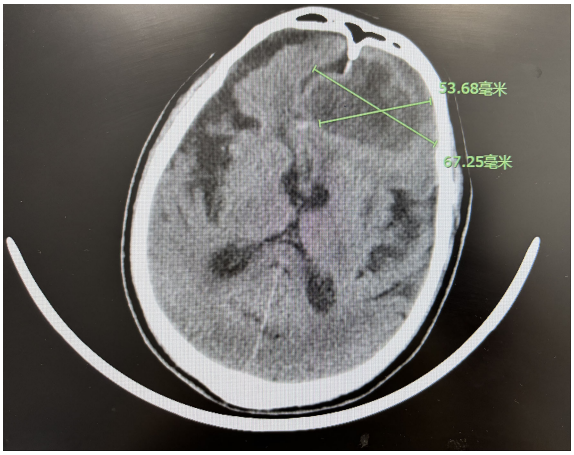


FIGURE 6
Head CT on 14 February 2025 (2 months of treatment). The lesion is stable, with partial absorption of hemorrhage and reduced edema.

For valproic acid, 0.4 g per dose, three times daily, was administered via gastric tube (for both anti-epileptic and epigenetic sensitization).

Supportive therapy included mannitol 125 mL every 12 h via intravenous infusion and dexamethasone 2.5 mg once daily as a low-dose corticosteroid to reduce peritumoral edema. Concurrent anti-infection therapy, gastric mucosal protection, total parenteral nutrition support, high-flow oxygen therapy, and continuous vital-sign monitoring were provided. These symptomatic interventions, such as corticosteroids and dehydration, may improve peritumoral edema and influence the evaluation of imaging-based treatment efficacy.

The patient was elderly, lethargic, bedridden, and critically ill, with extremely high transport risk, making MRI examination impossible. Therefore, all efficacy evaluations in this case relied

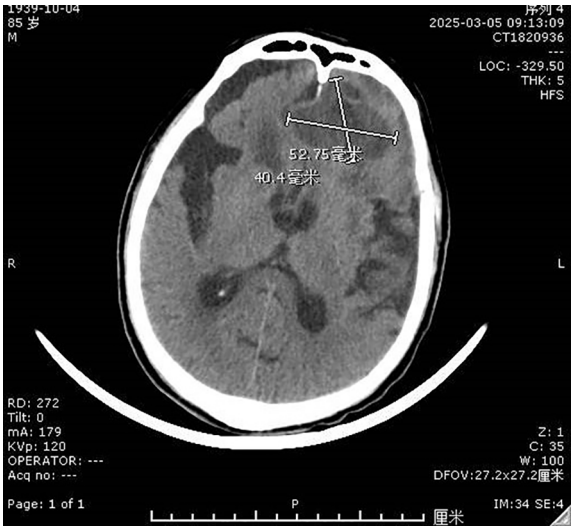


FIGURE 7
Head CT on 5 March 2025 (last follow-up). There was no progression of the lesion, and the edema was reduced, with the patient's condition remaining stable.

solely on serial head CT scans, and the internationally accepted MRI-RANO tumor response criteria could not be applied.

2.4 Follow-up and outcome

14 January 2025: Head CT showed stable tumor size, with intratumoral hemorrhage and intracranial air absorption compared to previous scans.

5 March 2025 (last follow-up): Head CT showed stable lesions without progression.

Safety follow-up: Regular blood routine and liver and kidney function tests throughout the entire period showed no grade III or above bone marrow suppression; no liver or kidney function impairment; and no drug-related rash, vomiting, or other adverse reactions; epilepsy was completely controlled.

Physical improvement: ECOG score improved to 3, KPS score improved to 50; consciousness and communication abilities improved.

Patient subjective condition: The patient's family reported reduced lethargy, ability to give simple responses, increased food intake, and a decreased daily care burden.

3 Discussion

For elderly frail patients with GBM receiving best supportive care alone, median survival is only 3–4 months (11, 12); metronomic temozolomide monotherapy can extend this to 6–9 months but with a higher risk of hematological toxicity [13,14]. In this case, an 85-year-old patient with a large hemorrhagic GBM and multiple severe comorbidities achieved 3 months of stable disease and improved physical condition with low-dose temozolomide combined with VPA, without severe adverse reactions. It should be noted that supportive therapies such as endoscopic surgery decompression and corticosteroids + mannitol dehydration can alleviate peritumoral edema and neurological symptoms, and clinical benefits cannot be entirely attributed to chemotherapy drugs.

Regimen rationale: MGMT promoter methylation positivity indicates sensitivity to temozolomide (6, 7). Low-dose metronomic temozolomide reduces bone marrow suppression and organ toxicity, suitable for very elderly patients. VPA acts as an HDAC inhibitor and epigenetically downregulates MGMT, thereby enhancing the killing effect of temozolomide, while also controlling epilepsy. Preclinical studies have confirmed the synergistic antitumor effects of this combination in gliomas (8–10).

Clinical significance: Low-dose temozolomide combined with VPA provides a low-toxicity, practical palliative treatment option for very elderly GBM patients with MGMT promoter methylation, frailty, and an inability to tolerate standard therapy (1–5).

3.1 Study limitations

This is a single retrospective case report with only one sample, limiting the level of clinical evidence.

The follow-up period is only 3 months, lacking long-term survival and long-term adverse drug reaction data.

Because of the patient's physical condition, MRI was unavailable, and efficacy evaluation relied solely on CT, reducing the accuracy of efficacy assessment.

Concurrent use of surgical decompression, corticosteroids, dehydration drugs, and other supportive measures makes it difficult to isolate the true anti-tumor effect of chemotherapy alone.

Given the lack of long-term follow-up data, large-sample prospective studies are needed to optimize VPA dosage and validate the efficacy of the combination regimen.

3.2 Study advantages

This case is a rare instance of a very elderly patient with multiple comorbidities and GBM, exploring a palliative regimen of metronomic temozolomide combined with VPA, providing real-world clinical reference data for similar elderly patients unable to tolerate standard chemotherapy and radiotherapy.

4 Conclusion

Low-dose metronomic temozolomide combined with VPA offers advantages of good safety, tolerability, and short-term disease stabilization in an 85-year-old frail patient, with MGMT-methylated GBM who was unable to tolerate standard surgery, chemotherapy, or radiotherapy. Limited by single-case data, this epigenetic sensitization strategy can only serve as an individualized palliative reference regimen and cannot be widely promoted; further clinical studies are needed to validate its efficacy.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

This case report was conducted in accordance with the Declaration of Helsinki. Ethical approval was waived by the Institutional Review Board/Ethics Committee of the Third People's Hospital of Hubei Province due to the retrospective nature of the case report and the minimal risk to the patient. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LG: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. YM: Supervision, Project administration, Writing – review & editing, Validation.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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