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Prolonged Partial Response to Bevacizumab and Valproic Acid in a Patient With Glioblastoma

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INTRODUCTION

Glioblastoma is the most common and malignant type of primary CNS tumor.^{1,2} The estimated median overall survival (OS) duration ranges from 14 months to 16 months, whereas the 5-year OS rate is estimated to be 5%.^{1,3–5} Chemoradiation followed by adjuvant temozolomide remains the standard frontline therapy.³ Bevacizumab has been used as a single agent or in combination with other agents at the time of diagnosis or at disease

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progression.^{6–11} In patients with newly diagnosed glioblastoma, the addition of bevacizumab to standard treatment regimens did not improve OS, which has resulted in limited use.¹¹ In recurrent glioblastoma, bevacizumab monotherapy was associated with higher rates of response (28%) and 6-month progression-free survival (PFS; 29% to 43%) compared with historical data with radiotherapy and other regimens (4% to 9% and 9% to 21%, respectively).¹¹ In recent years, immunotherapy has demonstrated promising results in selected patients, although long-term OS data are unavailable.^{12–16}

Valproic acid is a histone deacetylase inhibitor (HDI) that has antitumor activity associated with antiangiogenic effects.¹⁷ In in vitro and in vivo animal models, HDIs upregulated p53 and Von Hippel-Lindau and downregulated HIF-1 α and vascular endothelial growth factor (VEGF), which inhibits angiogenesis.¹⁷ HDIs also inhibit VEGF-stimulated endothelial cells and angiogenesis, and their anti tumor activity increases in combination with a VEGF receptor tyrosine kinase inhibitor.¹⁸ We have previously reported on the safety of bevacizumab and valproic acid in patients with advanced cancer.¹⁹

Here, we present a patient with progressive glioblastoma in whom prolonged partial response (PR) was achieved with bevacizumab and valproic acid. The patient's tumor tissue was retrospectively molecularly profiled to identify molecular alterations.

CASE PRESENTATION

A 53-year-old man presented in June 2011 to the emergency department of a community hospital with a 2-month history of progressive expressive dysarthria. Magnetic resonance imaging (MRI) of the brain revealed a 5.1-cm mass in the left parietal lobe, peripheral enhancement with edema, and mass effect on the left lateral ventricle. Surgical tumor biopsy confirmed the diagnosis of glioblastoma multiforme.

The patient had a history of hypertension and Gilbert syndrome. His surgical history included lumbar laminectomy for a herniated disk at the lumbar 5-sacral 1 joint and carpal tunnel release. The patient had a 4-pack-year smoking history and a history of social drinking. His father and brother died of lung cancer. In July 2011, the patient underwent a partial tumor resection followed by intensity-modulated radiation therapy (total dose, 59.4 Gy in 33 fractions; completed September 2011) with concurrent administration of temozolamide. MRI of the brain in September 2011 demonstrated disease progression and temozolamide was discontinued.

In November 2011, the patient referred himself to our phase I program and was enrolled in a clinical trial of a poly (ADP-ribose) polymerase inhibitor and temozolamide. Imaging studies demonstrated progressive disease after two cycles of therapy. In February 2012, he underwent a left temporal parietal craniotomy for tumor resection, which was complicated by inflammation of the surgical site that required oral antibiotics. In March 2012, the patient was enrolled in a clinical trial of a phosphatidylinositol-3 kinase inhibitor at another center. During cycle 1, inflammation of the surgical site worsened and a brain MRI revealed fluid collection below the bone flap. Fluid was drained and intravenous (IV) antibiotics were administered for 4 weeks followed by oral antibiotics for 6 weeks. No organism was

isolated. After three cycles, treatment with the phosphatidylinositol-3 kinase inhibitor was discontinued because of disease progression.

In June 2012, the patient returned to our clinic and was enrolled in a clinical trial of bevacizumab, temsirolimus, and valproic acid ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01552434) identifier: NCT01552434). Bevacizumab 5 mg/kg was administered IV on days 1 and 15, valproic acid 5 mg/kg orally once per day, and temsirolimus 20 mg IV once per week. Cycles were repeated every 28 days. After cycle 1, the patient developed ecchymosis and grade 1 thrombocytopenia. Temsirolimus was discontinued to decrease the probability of brain bleeding. In August 2012, MRI of the brain after two cycles of treatment demonstrated PR to treatment (Fig 1). The patient underwent speech therapy and his dysarthria improved.

The patient has tolerated treatment with bevacizumab and valproic acid well overall and is monitored closely by nephrologists and cardiologists. He required interruption of bevacizumab after cycle 33 because he underwent transurethral prostate resection as a result of an abscess that was not responding to drainage or IV antibiotics and after cycles 44 and 55 because of transient grade 2 proteinuria. During treatment with bevacizumab and valproic acid, the patient developed transient grade 2 thrombocytopenia, neutropenia, and hypertension. He has also developed mucositis, skin rash, peripheral neuropathy, and renal insufficiency—all grade 1, reversible. As of July 2018, the patient had received 70 treatment cycles without evidence of disease progression and was still undergoing treatment. In June 2018, molecular profiling was retrospectively performed on the patient's tumor tissue obtained in July 2011 using a 595-gene panel (Table 1).

DISCUSSION

Despite various treatment options, the prognosis of patients with advanced glioblastoma is poor.²² The efficacy of standard treatments is suboptimal and patients are encouraged to participate in clinical trials. Our patient experienced prolonged PR to bevacizumab and valproic acid, lasting for more than 6 years. His tumor had multiple alterations, including cyclin-dependent kinase 4 (CDK4) amplification and FGFR3-TACC3 chromosomal fusion.

Glioblastomas harbor several molecular alterations implicated in the activation of oncogenic pathways.^{23–25} Amplification of CDK4—located at chromosome 12—is common in glioblastoma,^{26,27} and its incidence was 13% in a comprehensive analysis.²⁵

Our patient was treated with valproic acid, which suppresses CDK4, among other proteins, and induces growth inhibition, apoptosis, and senescence in medulloblastoma cell lines.²⁸ Valproic acid was demonstrated to inhibit the proliferation of MCF-7 breast cancer cells via apoptosis and G1 phase arrest, possibly by downregulating cyclin D1,²⁹ which, in turn, decreased CDK4 protein levels.³⁰ Other investigators demonstrated that valproic acid significantly reduced mRNA expression of cyclin D1 and CDK4 in leukemic cells used in a murine xenograft tumor model, which leads to G₀/G₁ arrest.³¹ CDK4 amplification was found in tumors with FGFR3-TACC3 fusions and it was more frequent in isocitrate dehydrogenase wild-type gliomas that harbored FGFR3-TACC3 fusions than in those without the fusion.³²

The FGFR3 gene fuses with multiple partners, including the TACC3 gene, which encodes a protein that participates in the stabilization of the mitotic spindle. Incidence of FGFR3-TACC3 fusion in glioblastoma is 1.3% to 8.3%.^{32–35} This fusion increases FGFR signaling^{36,37} and thus regulates cell growth, differentiation, and tumor neoangiogenesis.^{38–40}

Our patient was also treated with bevacizumab, an anti-VEGF agent. By blocking VEGF activity, bevacizumab reduces vasogenic brain edema and inhibits tumor growth. A randomized phase TTT study (EORTC 26101) in patients with glioblastoma who experienced disease progression after chemoradiation demonstrated that there was no difference in OS between patients who received bevacizumab and lomustine compared with lomustine alone (hazard ratio, 0.95; 95% CI, 0.74 to 1.21; $P = .65$)⁸; however, the addition of bevacizumab to lomustine increased PFS from 1.5 months to 4.2 months (HR, 0.52; 95% CI, 0.41 to 0.64). A randomized phase TT trial of patients with glioblastoma at first recurrence after temozolomide chemoradiotherapy demonstrated that the 9-month OS rate was 43% (95% CI, 29% to 57%) in patients who were treated with lomustine, 38% (95% CI, 25% to 51%) in patients who were treated with bevacizumab, and 63% (95% CI, 49% to 75%) in patients who were treated with both.⁹ In a retrospective analysis of 310 patients with glioblastoma who were treated from 2010 to 2014, median OS duration was 13.1 months (95% CI, 11.5 to 14.6 months).⁴¹ In a multivariable analysis of patients with isocitrate dehydrogenase wild-type tumors, exposure to bevacizumab was not associated with OS.⁴¹

Multiple immunotherapeutic strategies are being developed for recurrent glioblastoma with encouraging results. Chimeric antigen receptor-engineered T cells that target the tumor-associated antigen interleukin-13 receptor $\alpha 2$ induced a complete response that lasted 7.5 months in a patient with recurrent glioblastoma ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02208362) identifier: NCT02208362).¹⁴ In a phase TT trial, depatuxizumab mafadotin M, a tumor-specific antibody-drug conjugate, combined with temozolomide improved OS compared with lomustine and temozolomide in patients with epidermal growth factor receptor-amplified recurrent glioblastoma.¹⁶ The programmed cell death 1 inhibitor nivolumab, with or without the cytotoxic T lymphocyte-associated protein 4 inhibitor ipilimumab, was associated with a PR rate of 7.5% and disease stabilization for greater than or equal to 12 weeks of 20% in patients with recurrent glioblastoma ($n = 40$).¹³ In a retrospective analysis of 50 patients with high-grade gliomas who received nivolumab after failure of radiation and chemotherapy, the median PFS and OS were 4.3 months and 6.5 months, respectively.¹² In 61 patients with recurrent supratentorial glioblastoma who were treated with convection-enhanced, intratumoral delivery of the recombinant nonpathogenic polio-rhinovirus chimera, 3-year OS rate was 21%.¹⁵

In conclusion, the combination of bevacizumab and valproic acid induced a prolonged PR in our patient with recurrent glioblastoma with CDK4 amplification and FGFR3-TACC3 chromosomal fusion. These drugs target multiple pathways associated with tumor progression and angiogenesis. Patients with glioblastoma should undergo tumor molecular profiling and immune marker analysis, and these results should be used to optimize

treatment selection. Circulating tumor DNA analysis is evolving as a noninvasive test to monitor tumor molecular alterations of patients with glioblastoma.

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Fig 1.

Magnetic resonance images of the brain [T1-weighted imaging post gadolinium contrast; axial plane (A and B), coronal (C)] at (1) baseline and (2) after first restaging after two cycles of treatment with bevacizumab and valproic acid. Images show enhancing tumor (arrows) surrounding a resection cavity in the left parietal lobe. A 34% decrease in tumor burden by RECIST criteria (Response Evaluation Criteria In Solid Tumors)²⁰ and 55% decrease by Response Assessment in Neuro-Oncology criteria²¹ indicate partial response.

Table 1.

Next-Generation Clinical Sequencing Report by Tempus (June 2018)

Biologically Relevant Variant	Variant of Unknown Significance
CDK4 amplification	MLL2 p.R5159Q
FGFR3-TACC3 fusion	IL2RA p.T271K
SMARCB1 p.E98fs	FCGR2A p.R264C
TERT c.-124C>T	ETV6 p.S30W
CUX1 c.63+1G>A	Ki-67 p.M961del
CHD2 p.K1391fs	MLH3 p.P1148L
ETV6 p.M240fs	KMT2B p.Q881*
Tumor mutational burden: High (13.3 nonsynonymous mutations/megabase)	
Microsatellite stable	

NOTE. Genomic testing was performed at Tempus using the Tempus xT Oncology Assay, which is a 595-gene targeted sequencing panel. Formalin-fixed, paraffin-embedded samples were sequenced to detect somatic single-nucleotide variants, insertion-deletions, copy number variants, gene rearrangements, and microsatellite instability. Detected variants are categorized as either somatic or germline. We also performed a Tempus RNA whole-transcriptome panel and used this for expanded detection of gene rearrangements, immune infiltration, and gene expression for immune and targeted therapy related genes.

Abbreviation: CDK4, cyclin-dependent kinase 4.